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Chronic Nonvalvular Cardiac Disease or Chronic Myocardial Insufficiency and Its Therapeutic Management*

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In an adult clinic more patients with cardiac disease without valve lesions are seen than those with valve lesions. Rheumatic fever is the largest cause of valvular disease, and this is chiefly a disease of childhood and early adult life. In children's clinics, apart from congenital heart disease, other than rheumatic valvular disease of the heart is unusual. The majority of patients with rheumatic heart disease die within a twenty year period of the inception of their heart lesion, and they have had the causative rheumatic fever in childhood. The result is a rapidly falling curve of incidence of rheumatic heart disease in hospital admissions in the years following the age of thirty.

Syphilis almost never causes any other form of heart disease than the aortic insufficiency associated with syphilitic aortitis or aneurysm. This, next to rheumatic fever, is the most frequent cause of valvular disease of the heart. The average time between causative infection with the spirochetes of syphilis and the evidences of aortic disease is between fifteen and twenty years. Syphilitic infection is, as very aptly has been said, an incident in the bloom of youth. Certainly many syphilitic infections do begin before twenty-five. After the aortic lesion of syphilis has advanced to the stage of causing symptoms, life on the average is considerably under five years. These factors give us a rapidly falling curve of incidence of admissions to hospitals of patients with syphilitic aortic insufficiency following the forty year period of life.

After the forty year age level, hospitals have usually an increasing rather than a decreasing rate of admissions for cardiac disease, and these patients far more often than otherwise have neither the valve lesions of rheumatic heart disease nor the aortic lesions of syphilis.

As a result of examination, we know that, as a rule, these patients show the history and findings indicative of a failing circulation, symptoms and signs all too familiar for me to burden you with them; the heart with rare exceptions is enlarged, as usually can be detected by simple physical examination, but which in the obese and the emphysematous may require x-ray observation for its detection;

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heart sounds and rhythm may be normal or abnormal; murmurs may be lacking, or some sort of a systolic murmur, ordinarily loudest in the apex region, may be heard.

In the rheumatic group and in the syphilitic group of patients with heart disease disturbances of valve function play an important part in causing cardiac failure. In the rheumatic group it is notable that, when symptoms of cardiac failure develop, there are in most patients well marked signs of mitral stenosis with or without auricular fibrillation. In the syphilitic group it is very striking how little cardiac enlargement there is with aortitis and aneurysm until the aortic valve becomes incompetent, and as a rule, only after these developments do we have evidences of circulatory failure. It seems reasonable to speak of both these groups as forms of chronic valvular cardiac disease.

In contrast is the striking absence of evidence of valve lesion, when one examines the heart in a patient of this past-forty group who has had neither rheumatism nor syphilis. Whether the systolic apical murmur is prominent or not seems to play little part in the degree of observed evidences of heart failure. Why not then, in contrast, speak of these as chronic non-valvular cardiac disease?

In all three of these groups the clinician, if he has had opportunity to study carefully the patient prior to the last day or two of life, can describe with very considerable accuracy what the post-mortem examination will reveal. In few realms of medicine come so few surprising revelations by the pathologist. The predicted mitral stenosis is revealed and other valve lesions, notably aortic ones, appear or not, as anticipated in the rheumatic group; the chief failure in clinical diagnosis concerns the tricuspid valve, which may show, though rarely, an unpredicted stenotic lesion. The predicted aortic lesion with incompetent aortic cusps is as expected in the syphilitic group. In the third group, the non-valvular group, is revealed, as predicted, the cardiac enlargement without other valve lesion than the enlarged orifice resulting from dilatation of the ventricles.

The clinician and the pathologist are in accord as to the rheumatic and syphilitic etiologies. If there has been clinical doubt, and there often is, as to the etiology in the third group, the pathologist very often fails to clear the doubt. Pathological study usually confirms the ideas derived by the clinician from his examinations of the patient during life; quite rarely does it add anything of importance to those ideas.

In the first and second groups (rheumatic and syphilitic) it seems reasonably certain that a disease process of known etiology has led to organic lesion of the heart valves, and that the consequent disturbance in cardiac function has played a significant part in the progressing disease with final death of the patient.

In the third group it seems equally certain that there has been no organic lesion of the heart valves and that such failure to function on the part of the valves, as has occurred, is purely secondary to the dilatation of valve orifices resulting from dilatation of cardiac cavities. Careful study of this

third group of patients has not shown any etiological factor in evidence for all of the group, nor has it revealed any pathological lesion which consistently will explain the progressing cardiac failure that has led to the patient's death. In the gross the heart muscle looks strikingly well nourished, is normal in color and appears powerful as a muscle. In some, microscopic examination will show various types of degeneration of muscle fibres and nuclei, but these obviously are of recent origin and could have no great influence in determining a cardiac failure which has increased progressively for months or even years. As a rule the muscle fibres are larger than normal. At times coronary arteries will show considerable narrowing of the lumen indicative of a lessened nutritional circulation, but just as often this is not present (none or slight in 36.9 per cent, moderate in 28.3 per cent and marked in 35.1 per cent of 228 hearts studied at autopsy).* In some there is a diffuse fibrosis, but this definitely is unusual, and incidentally such cases differ in no wise clinically from those without diffuse fibrosis. Focal fibrosis of microscopic proportions is found more frequently (fibrosis, none or slight in 68.6 per cent, moderate in 22.5 per cent and marked in 8.9 per cent of 228 hearts studied at autopsy). There may be pathological changes in the small, terminal branches of the coronary arteries (none or slight in 48.2 per cent, moderate in 34.1 percent and marked in 17.7 per cent of 228 hearts studied at autopsy). Often both types of sclerosis of vessels are lacking. Cellular infiltration, usually focal, occurs but is neither extensive nor frequent. In a goodly proportion of these hearts histological study shows no lesion that in its extent of distribution conceivably could explain the obvious fact that the patient has died of cardiac failure (50 out of 223 hearts), while in many others the pathological lesion scarcely seems causative of observed symptoms. A minute knowledge of the architecture of the muscle of the heart throws no light on how small focal lesions could incommode seriously the function of the heart muscle. Conceivably focal lesions might inaugurate damaging arrhythmias, but if these develop, they are relatively late in their appearance, and often these patients died without ever showing any arrhythmia.

From the clinical study of these patients it is obvious that syphilis plays no important etiological rôle; very rarely it may be a cause. Rheumatic fever certainly does not cause the disturbance. Focal infection may, at times, be a cause, but there is no satisfactory proof of this. No evidence incriminates any other infection. Definite endocrinopathies, except occasionally thyroid disturbances, are of no causative significance. In one-half to two-thirds of these patients hypertension with or without arteriosclerosis and with or without nephritis is or has been present. When it exists, it certainly would seem to be at least a contributory, if not the chief cause, and yet there are many unanswerable riddles, as we watch the progress of cardiac disability in the patient with

*These statistical studies were made at the Peter Bent Brigham Hospital by Greene FitzHugh, New England Journal of Medicine, 1930, ccciii, 201.

hypertension. Cases in every way identical with those of later life occasionally are observed at birth and in early childhood, so the aging process does not serve as a satisfactory cause.

It is very striking how definite and convincing is our knowledge of what is going on, and why, in the rheumatic and syphilitic group, in contrast to its uncertainties and unconvincingness in regard to this third, or non-valvular, group.

From what has been said, it is clear that, with our ignorance as to etiology in this group of non-valvular cardiac patients, methods of prevention will not be helpful in our management. The only cases with any very constant accompaniment of anything of possible etiologic significance is the hypertensive group. Assuming that in these hypertension is the cause, which may not be the case, how little does that help so long as we remain in the present state of uncertainty as to methods of controlling hypertension. We can lessen added stresses and strains but do little more than this. In those definitely of thyroid origin, the plan of treatment is directed to restoration of thyroid function to a normal level and that is not difficult. Definite foci of infection should be eliminated whenever possible; even if not etiologically important in the cardiac lesion, it is helpful to the patients' general condition to eradicate them. Indiscriminate removal of tonsils and teeth, drainage of sinuses, etc., because they might be foci of infection, is reprehensible, though a frequent practice, as judged from what has happened in patients that I subsequently see. Excesses in food and drink are to be avoided; many vagaries of diet are advised by food faddists which run from nothing but grapes to almost nothing but sunkist oranges through purely vegetarian, largely meat, fat-poor, salt-poor, vitamin-rich, sugar-poor, carbohydrate-rich, and only milk and largely nut diets with the expectancy that soon some one will exploit a blubber diet which seems consistent only with life in the arctic or antarctic region, all of which dietary regimes seem to succeed in ratio to the psychological influence of the advisor and the psychopathic complex of the advisee. Excesses of weight should be reduced very gradually by food restrictions alone; one pound per week is my advised rate for the ambulatory patient.

A readjustment of mental and physical activities in accordance with circulatory disability helps much with these patients, whether they show little or much evidence of circulatory malfunction. When symptoms develop, rest with digitalis should be instituted and then a gradual return to a modified amount of activity. Increasingly I advise these patients to take continuously a daily dosage of digitalis, for most patients the equivalent in digitalis value of 0.1 gram of powdered leaves; the preparation of digitalis used seems to me to be immaterial provided it is an efficient preparation. Some patients will not tolerate 0.1 gram per day; they should have less in accord with their determined tolerance. I believe patients, who have had only the slightest evidences of cardiac inefficiency, profit from such continued digitalis ingestion. There seems some sound evidence for

the belief that digitalis dosage might well be commenced when cardiac enlargement is detected, even though no symptoms of cardiac insufficiency have yet appeared. The belief that digitalis is useful only in the presence of auricular fibrillation seems still to persist, though there is much very striking clinical evidence against it, especially strong for this particular group of patients.

Terminology for this group of patients is confused. Chronic non-valvular cardiac disease seems to me a good term. Chronic myocardial insufficiency is not unsatisfactory. Chronic myocarditis, too, would be satisfactory, if one will admit that it does not connote inflammation of the myocardium, but long usage renders that difficult. Any of these terms can be modified by adding an adjective descriptive of the cause, when known, such as hypertensive, hyperthyroid, etc. On the basis of present knowledge I prefer chronic non-valvular cardiac disease, if one speaks of the other groups as cases of chronic valvular cardiac disease.

Circulatory Adjustments in Heart Disease: A Concept of Circulatory Failure*†

By Soma Weiss, M.D., F.A.C.P., *Boston, Mass.*

INTENSIVE clinical and experimental studies of the heart and circulation during the past quarter century have shed considerable light on problems of the cardiovascular system. The accumulated facts, however, are of less aid in understanding the clinical picture of cardiac and circulatory diseases than one would expect. Discoveries with the galvanometer have revealed in detail the mechanism of various disturbances in the conduction of nerve impulses and in the excitability of the myocardium. Correlations between the clinical behavior of the patient and the electrocardiographic findings have made the clinical diagnosis of cardiac pathology more accurate than before; but, on the other hand, have disclosed little concerning the efficiency of the heart. The electrocardiogram is not a direct measure of the state of the circulation. A patient with auricular fibrillation, diagnosed as "pulsus irregularis perpetuus" during the Spanish-American War, is still at hard daily physical work. Another patient, showing a similar electrocardiogram, is dying with congestive failure of the circulation. Recently we observed a patient who maintained a fairly efficient circulation with ventricular tachycardia for thirty-five days and then reverted to normal sinus rhythm.

A majority of the symptoms and signs of the patient with cardiovascular disease depend rather on the state of the circulation than on the heart. Knowledge of the conditions underlying the clinical picture of circulatory failure is still exceedingly meager. We have no satisfactory explanation of why one patient develops an early hydrothorax, while another dies of massive peripheral edema with no trace of fluid in the pleural cavity. The interpretations of the correlation of the clinical manifestations of heart disease are but empirical and often confusing.

It is not surprising that progress in this branch of medicine has lagged behind, for the factors which determine the clinical picture of circulatory failure are numerous and variable. They may be present in many different combinations. Compensatory factors frequently counteract and thus obscure

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unfavorable changes. Furthermore, not only are there various changes and adjustments present in different types of heart disease; but in different stages of the same type of heart disease, new factors, or different combinations of factors, may be responsible for the same clinical manifestation. To understand circulatory failure, a study of the patient with a correlation of the combined chemical, physiological and morphological factors, instead of a separate analysis of single aspects, is especially important. Chemistry, physiology and anatomy are dependent on each other; they may be separated successfully in theory but are combined with equal importance in practice.

From the available evidence it is thus difficult to construct as yet an accurate and detailed picture of the sequence of events in the progress of circulatory failure. The difficulty is great not only because numerous gaps exist at the most crucial points of the problem, but also because results of the investigations are often contradictory even concerning the most diligently studied aspects of the circulation. A concept, therefore, which attempts to correlate the clinical picture with the functional and structural changes of circulatory failure can be at its best, but incomplete. Nevertheless, it is desirable from time to time to assemble the scattered blocks of knowledge and then inspect them from a distance in the hope that they may assume the outlines of a real structure, even though broken by spaces. Such a concept, despite its incompleteness, helps in the estimation of the clinical condition of the patient and in the proper application of therapeutic measures.

In the course of this limited discussion it is impossible to enter into an intricate interpretation of the individual symptoms and signs of circulatory failure. The following presentation will therefore be limited to those alterations of circulatory function which bear closely on the clinical manifestations of circulatory failure. Factors referable to the heart will not be discussed. Correlations of the circulatory functions are presented partly from clinical observations and investigations conducted in the Boston City Hospital during the past five years, and partly from the results obtained by other investigators. Occasionally, when reliable observations on man are not available, analogous experimental observations on animals are used. It is hoped that clinical studies in progress will yield more direct proof on these points. Controversial discussions will be omitted.

1. Heart Disease and Circulatory Failure

Whenever the circulation fails to accomplish its task of efficiently supplying the tissues with nourishment and promptly eliminating the waste products of cell metabolism during the normal activities of life, we speak of circulatory failure. Normal circulatory efficiency, like so many other biological functions, is a broad average since considerable variation exists among healthy individuals. Heart disease may coexist with a circulation normal in every respect for years. Often, however, long before actual impairment of the efficiency of the body

occurs, alterations and adjustments take place in various parts of the circulation. Thus, for example, a patient may perform normal amounts of daily work, but accomplish this with a higher expenditure of cardiac energy, an increased ventilation of the lungs, a higher arterial blood pressure, and an increased utilization of oxygen and exchange of other substances between the capillary blood and tissue cells. These adjustments make it possible for the patient to perform vital functions which otherwise could not be carried on.

In the presence of heart disease the nature of the readjustment of the circulation depends to a certain degree quantitatively and qualitatively on the localization and etiology of the cardiac lesions. However, failure of the circulation may be independent of heart disease. For this reason, it is erroneous to speak of heart disease and circulatory failure interchangeably. Circulatory failure often results from primary derangement of the vasomotor system. Such is the case in the progressive vasomotor collapse (shock) which follows surgical operations and other types of trauma, in certain diseases of the nervous system, infectious diseases and toxemias. The clinical picture of vasomotor collapse is quite distinct from that of congestive heart disease. The patient is pale; dyspnea may be present but without orthopnea; the veins are collapsed instead of being dilated; the circulating blood volume is early reduced, due to stagnation of blood in the peripheral minute vessels. Correspondingly, there is a decrease in the minute and stroke volume output of the heart; and as a result of this, the venous and arterial blood pressures fall below normal although the mean velocity of blood flow may be unaltered[1,2]. There is a depletion of the blood content of the large vessels and chambers of the heart, and an overfilling of the peripheral minute vessels due to purposeless relaxation of the arterioles and perhaps other minute vessels. The heart expels with ease whatever blood reaches its chambers.

Vasomotor collapse does not always exist in this pure form, as the chemical factors which cause the collapse may also depress the heart function. This may be the case in lobar pneumonia. In such instances the clinical picture and the type of circulatory failure depend on a combination of vasomotor collapse and heart failure.

Certain investigations have suggested that primary changes in the peripheral circulation are also responsible for the failure of the circulation in heart disease. Thus it has been claimed that primary disturbances in the lactic acid metabolism cause important changes in the peripheral vascular system and precipitate the sequence of events that results in circulatory failure. A recent investigation in the Boston City Hospital fails to support this claim. No primary disturbances of the lactic acid formation before the appearance of an inadequate blood flow could be discovered. All the evidence obtained by us thus far supports the logical concept suggested by clinical manifestations and post mortem findings, that local disturbance of the heart is primarily responsible for the circulatory changes[3].

The clinical picture of circulatory failure varies, depending on the etiology of the heart disease and the seat of the lesions. Because the cardiac lesions are rarely in pure form and the size and rate of their development are usually unknown factors, the clinical picture of failure varies considerably even in a group of patients with similar morbid changes in the heart, so far as can be judged from clinical observations.

In this presentation, for the sake of simplicity, the circulatory adaptations will be correlated, as a rule, with the normal basal metabolism at rest. In reality the circulatory efficiency can be considered as an index between efficient capillary blood supply and tissue metabolism. This index may be disturbed both by abnormal changes of the circulation or by increase in metabolism. For obvious reasons, in the presence of markedly increased metabolism a relatively slight circulatory failure leads to severe clinical disturbances. Clinical symptoms and signs are often the expressions of an altered balance rather than absolute deviations from normal. In addition to changes in the heart, numerous extracardiac factors may influence the circulation and thus the clinical picture. Of these factors, fever of bacterial or non-bacterial origin; altered hemoglobin and protein content of the blood; pulmonary pathology, especially emphysema and bronchitis; and internal secretory disturbances are most important. The way in which these factors influence, at times fundamentally, the circulation cannot be discussed here.

II. Early Stages of Circulatory Failure

"Congestive heart failure" with dyspnea and orthopnea at rest, râles over the base of the lungs, hydrothorax, enlarged liver, ascites, and dependent edema is usually the end picture of chronic disease of years' duration. For a long period before this stage of circulatory failure is reached the patient is comfortable at rest and develops circulatory embarrassment only after exertion. At this stage, the patient with heart disease differs apparently from normal subjects only in the degree of muscular activity that brings on dyspnea and weakness. This early stage is the longest period in the natural course of heart disease, and it is in this stage that intelligent preventive measures will ameliorate and prolong the life of the patient. Unfortunately, this period of circulatory failure is most incompletely understood.

At the onset of circulatory failure the symptoms and signs are referable almost entirely to local disturbances in cardiac function. The main symptom referable to the circulation is dyspnea; and it is the mechanism underlying this dyspnea that is the center of the problem. If one examines the state of the peripheral circulation at this stage one finds that the arterial, capillary and venous blood pressures are unaltered. The cardiac output per minute may be normal or slightly reduced[4,5]. The velocity of blood flow as observed in the capillaries of the finger nail bed[6] as well as in the large veins of the forearm[7] is frequently normal. Hence the velocity in the

arteries must also be unaltered. Similarly, the arterio-venous oxygen differences of the arms and legs and the lactic acid content of the arterial and venous blood are normal[3]. In other words, all the studies with available methods indicate that the blood supply of the organs is adequate and normal at rest. Even more significant is the fact that if a patient performs a walking exercise sufficient to induce dyspnea, and the arterio-venous oxygen differences are studied by repeated punctures of the femoral and cubital veins, not only the volume difference of oxygen but the rate of the return of the oxygen difference to normal is the same in cardiac patients with dyspnea as in the normal subject who experiences no difficulty in performing the same exercise[3]. It is also significant that the curve of the lactic acid content of the blood in the femoral vein after exercise shows the same rise and return to normal as that of normal individuals. There is no difference in the lactic acid overflow into the blood from exercised muscle in the dyspneic cardiac patient and in the normal subject who experiences no dyspnea[3]. These recent observations indicate that in the early stages of circulatory failure, when the patient becomes dyspneic after mild exercise, the peripheral supply of blood to the tissues may still be adequate and the lactic acid formation in the exercising muscle not disturbed.

What, then, are the factors which show deviation from normal at this stage? One does find early a reduction of the vital capacity of the lungs[8,9]. Simultaneously, or somewhat later, the blood flow through the lungs is retarded. If the total lung volume, as well as the interrelation between various portions of the respiratory space are measured, one finds that the total lung volume is normal or may even be increased[10,11]. The residual air, instead of being decreased as one would expect from the diminished vital capacity, may be increased both relatively and absolutely, often at the expense of the reserve air, which decreases. A disproportion therefore develops between the residual air and the reserve air[11]. Unfortunately, no observations on the pressure relations in the pulmonary circuit in man are available.

Is it possible to correlate these physiological observations with the structural changes and the behavior of the patient? It seems significant that all the abnormal findings observed in the early stages of circulatory failure bear on the pulmonary circulation and on the structural and physiological alterations of the respiratory surface while, on the other hand, the larger circulation shows no morbid changes. This obviously justifies two conclusions of great significance: (a) *that in early stages of circulatory failure changes occur in the pulmonary circulation*; and (b) *that changes in the pulmonary circulation may be independent of the larger circulation.*

In rheumatic, syphilitic, hypertensive and arteriosclerotic heart disease it is in the pulmonary venous system that the first effect of the heart disease manifests itself*. The back pressure

*Tricuspid disease without other vascular disease in rheumatic heart disease, and coronary sclerosis involving the blood supply of the right ventricle alone are of rare occurrence.

effect in cases of mitral disease and in cases of failure of the left ventricle is obvious. Its occurrence was claimed, long before the application of physiological concepts to clinical medicine, by morphologists of the 17th century. But the significance of this back pressure effect has not been examined in detail. If the left ventricle is not normally efficient and a certain amount of blood accumulates in the pulmonary vein, one or a combination of two possibilities may occur: (a) there being no essential alteration in the cross-sectional area of the vascular portion which offers the resistance to the right ventricle, *the increase in the pulmonary venous pressure will result in a proportional increase in the pulmonary capillary pressure, and later, in the pulmonary arterial pressure;* (b) *a considerable increase in the cross section and volume of the vascular bed of the pulmonary circuit may result without necessitating much alteration in pulmonary arterial pressure.* Teleological and experimental evidence strongly supports the presence of the second factor in early stages of circulatory failure.

It is now established that reserve capillaries exist in almost all the organs so far investigated. It would be most unusual if the lungs, the specific function of which depends entirely on capillary activity, did not possess such reserve capillaries. Their existence in the lungs has been suspected ever since the work of Cohnheim and Litten[12] in 1876. In rabbits, reserve capillaries which open during physiological activity were graphically demonstrated by Toyama[13] in 1925. In cats, the opening of new capillaries was observed by Wearn, Barr and German[14]. Hall[15] denies the appearance of new capillaries in the lungs with unchanged activity. He did not study the problem of reserve capillaries in the presence of various states of the circulation. Therefore the existence of reserve capillaries in the lungs can be considered as established.

Increase in the venous pressure is one of the most effective means by which reserve capillaries can be opened in the larger circuit. In human beings this can be demonstrated with surface capillaries of the skin[16]. Whether the opening of the capillaries induced by increased venous pressure is a passive phenomenon depending on the widening of the arterioles, or an active process; or whether chemical, physical or local reflex factors regulate their opening does not bear on the problem discussed here. The importance of the widening of the arterioles and the opening of new capillaries to the local maintenance and regulation of adequate peripheral blood flow in the presence of congestion in the peripheral veins has been repeatedly demonstrated and emphasized in recent years. We believe that *in progressive heart failure the pulmonary arterioles widen and a reserve capillary bed opens in the lungs; and that the mechanism of this process is governed by the same physiological laws as have been demonstrated in the peripheral circulation.* This concept is not only supported by a number of observations, but it explains several apparently contradictory and isolated observations previously not understood. Wearn and his associates[17] observed that new capillaries appear regularly when back

pressure is induced in the pulmonary vein by pressure over the aorta. Such pressure is more efficacious in opening the capillaries than increasing the blood flow and the pulmonary arterial pressure with adrenalin. In rheumatic heart disease and arterial hypertension a retardation of the maximal velocity of the blood flow through the lungs may occur with a normal or only slightly reduced cardiac output. In the later stages of circulatory failure again the degree of retardation of the blood velocity in the lungs is more marked than the reduction of the volume blood flow, as judged from the oxygen utilization in the upper and lower extremities[3]. This apparent discrepancy between the velocity and volume flow can be explained only by an increase in the cross-sectional area of the capillary bed. Such an increase may occur (a) through the stretching of previously opened capillaries, or (b) through the opening of new capillaries. The first possibility is not supported by experiments, and furthermore would be a purposeless and harmful mechanism. It would result in an early and marked increase in the pulmonary and capillary arterial pressure, which would soon damage the right ventricle and lead to pulmonary edema. Instead of one row, two rows of red corpuscles would pass through the capillaries, and this in turn would make the exchange of blood gases incomplete. As early as 1876, Lichtheim[18] showed that considerable occlusion of the left pulmonary artery fails to induce any appreciable alteration in the pressure of the right pulmonary artery or of the aorta. Lichtheim concluded, therefore, that the amount of blood flowing through the right lung was unaltered. He attempted to explain his observations on the basis of a compensatory increase in the diameter of the pulmonary artery.

Increase in the cross-sectional area may occur without any appreciable elevation in the resistance of the arteriolar and capillary beds of the lungs. All of these observations, therefore, indicate directly or indirectly that the increased cross-section develops through a widening of the arterioles and an opening of the reserve capillaries. A progressive increase of the capillaries makes it possible to maintain a normal or approximately normal volume of blood flow through the lungs per unit of time without much added burden to the right side of the heart. It is probably this mechanism which makes it possible for the patient with heart disease to live fairly comfortably for many years.

The opening up of numerous new capillaries along the alveolar surface and the moderately increased capillary pressure must have an important effect on the shape and consistency of the alveoli, which explains the stiffening observed experimentally by von Basch and his pupils some fifty years ago[19]. This dilatation and stiffening of the alveoli increases the residual air, relatively or absolutely, depending on whether or not the residual air increases at the expense of the reserve air of the lung. These changes in turn are responsible for the early decrease in the vital capacity. The reduction in the vital capacity, therefore, is not dependent on the encroachment of the blood on the alveoli, but rather on the development of *a functional*

emphysema of the alveoli induced by the opening of new capillaries under normal or higher than normal tension. The increased blood volume in the lungs does not decrease the total air space but rather causes the diaphragm and bony thorax to assume a slightly inspiratory position, thus allowing space for the increased total blood volume.

If one accepts this theory of the circulatory and respiratory mechanisms one can then clearly understand that the development of dyspnea in heart disease is primarily due to the active rôle of pulmonary arterioles and reserve capillaries and to a functional emphysema. It is also possible that loss of elasticity of the alveolar wall *per se* makes expiration difficult and thus adds to the subjective sensation of dyspnea. In the finer analysis of the mechanism of dyspnea, reflexes between the lungs and the respiratory center activated by the changes just described play an important rôle. Numerous animal experiments reported in the literature also support the contention that *dyspnea in the early stage of circulatory failure is produced through nervous communications between the pulmonary system and the medulla and not by local chemical changes within the respiratory center.* Finally, the concept proposed not only brings into harmony the apparent contradictory findings referable to the pulmonary circulation but also offers a rational explanation for the fact, repeatedly demonstrated experimentally on animals since Lichtheim's original studies[18], that the peripheral circulation may be normal despite changes in the pulmonary circulation and in the alveoli and pulmonary reflexes.

III. Later Stages of Circulatory Failure

In contrast to the early stages of circulatory failure, the later stages exhibit numerous *clinical manifestations.* With the progress of the dysfunction of the left ventricle, symptoms and signs of "congestive failure" gradually appear with cyanosis, râles over the base of the lungs, hydrothorax, dyspnea after slight or no exertion, orthopnea, increasing engorgement of the veins of the larger circuit, enlarged liver, ascites, peripheral edema and other well recognized clinical manifestations. Considerable variations occur clinically both in the appearance and the combination of these manifestations.

If one computes the various aspects of the circulation that have been *measured quantitatively in man,* one frequently finds the following sequence of changes. The vital capacity and the velocity of the blood flow become increasingly diminished[20]. These two measurements may deviate 100 per cent or more from their normal values. With these marked changes comes a tendency to a decreased cardiac output of blood. The decrease in the blood volume flow through the lungs is normally not as marked as the degree of slowing of blood flow. Simultaneously, the peripheral venous pressure rises steadily above normal values. Greater and greater amounts of oxygen are utilized in the capillary blood, which, while the body is in the upright position, may reach oxygen values of as high as 16 to 17 volumes

per cent after slight exertion[3]. If the congestion in the lungs is marked, difficulty in the areation of the blood reduces the oxygen saturation of the arterial blood. Only when the peripheral adaptations of the larger circulation have been exhausted do there develop, rather late in the natural course of circulatory failure, physicochemical disturbances of the blood, such as an increased lactic acid content, an altered buffer capacity, and changes in the hydrogen ion concentration. When these changes appear even at rest, the tissues of the entire body are severely affected in the performance of their necessary functions. Disturbances in the local or peripheral vasomotor reflexes are then an expression of extreme failure of the circulation.

The concept outlined in the previous chapter may be expanded even further, on the basis of the clinical observations and the quantitative measurements of the circulation during moderate or severe failure described above, in an attempt to obtain a more complete insight into the sequence of events. As the cardiac dysfunction progresses, the pressure in the pulmonary vein must rise further. This produces further compensatory dilatation of the pulmonary arteriolar system and hence an increase in the number of open capillaries. At the same time, in order that an adequate amount of blood should flow through the lungs, the pressure in the capillary bed must increase to correspond to the elevated pressure in the pulmonary vein. Considerable increase in the capillary pressure may occur without necessitating an increase of pressure in the pulmonary artery since the widening of the arterioles means that a relatively high arteriolar pressure is exerted increasingly on the capillaries, thus establishing an optimal or almost optimal pressure gradient between the capillaries and veins. In the previous study of the peripheral circulation[21] it was shown that by inducing a relaxation of the arterioles the capillary pressure might rise to such high values as from 46 to 65 mm. in normal subjects, and from 60 to 150 mm. in patients with hypertension. By analogy, it is possible that the pulmonary capillary pressure might rise to about 20 mm. of mercury through arteriolar regulation. Only when the compensatory arteriolar pressure is exhausted will the pulmonary arterial pressure have to rise to correspond to a further increase in the venous pressure. With these progressive changes in the pulmonary circuit, there must be an increasing stiffening of the alveoli and an increase in the total volume of blood in the lungs. This is obviously present, as indicated by post mortem observation. The diaphragm tends to fall, and thus, partly for mechanical, partly for nervous reasons, the rapid, shallow respiration of the cardiac patient becomes necessary. Obviously, changes in the lung function due to pathologic alterations in the pulmonary circulation are, disregarding chemical disturbances of the blood, the primary factors in the respiratory difficalty. The dyspnea of the cardiac patient at this stage is still a local pulmonary problem. (The reflex interrelation between the changes in the lungs and the respiratory center cannot be entered into here). Thus the cardiac patient with severe primary disturbances in the pulmonary

circulation behaves to a certain extent not dissimilarly to the patient with acute emphysema. This concept is further supported by the occurrence in the cardiac patient of a distinctive type of respiration, the inspiratory position of the thorax, and the low diaphragm which often retracts the lower costal margins during inspiration. It explains also why cardiac dyspnea is often associated with expiratory difficulties in contrast to the dyspnea which develops in patients without heart disease after central stimulation. In patients with emphysema the changes in the lungs are independent of the circulation; in cardiac patients they are secondary to it.

There is another important factor in circulatory failure. The pressure in the pulmonary vein, both in normal subjects and in patients with circulatory failure, depends on gravity. Just as in the larger circuit, gravity increases the pulmonary venous pressure progressively below the level of the left auricle. As long as the circulation is normal this factor plays no obvious rôle. However, if, as in advanced failure, the pressure in the left auricle increases considerably, the situation becomes quite different. Under such conditions the pressure over the lower portion of the pulmonary vein must be considerably higher than over the upper portion of the lungs. Indeed, over the base it may become so high that neither the arteriolar nor the arterial pulmonary pressure can raise the capillary pressure sufficiently to insure an adequate capillary blood flow. Considerable slowing of the blood flow in the base of the lungs must occur at this stage, while the flow over the upper portion of the lung must be more rapid. Finally, a stagnation of the blood flow results in "sedimentation of the blood" in the hypostatic portion of the lung leading finally to transudation of the serum. This "sedimentation of the blood" can be demonstrated by simple experiments in rabbits which are susceptible to postural changes from horizontal to upright position. It is this mechanism that produces clinical signs of pulmonary congestion.

Obviously, with the approach of pulmonary congestion, the vital capacity is diminished not only by the factors discussed in the previous section, but by the encroachment of stagnant blood on the alveolar spaces. This explains why measurements of the lung volume in this stage show a diminution of the total air spaces as well as of the residual air of the lungs[10].

The orthopnea in cardiac patients with clinical evidence of pulmonary engorgement, prolonged velocity, lowered vital capacity but no elevation in the venous pressure, is due partly to the same causes as emphysema or asthma, partly to the fact that upright posture may elevate a considerable portion of the lungs and make possible the maintenance of the pulmonary blood flow with less strain on the right side of the heart[22].

The consideration outlined clearly suggests the possibility that *a normal or decreased amount of blood may flow through the lungs under entirely different pressure relations within the pulmonary circuit. Thus the same minute volume of blood flow may represent different burdens for the right ventricle in different states of the cir-*

culation. This explains also the hitherto paradoxical observations that digitalis occasionally may benefit the patient without materially altering the cardiac output or velocity of pulmonary blood flow[4,23]. *The measurement of the amount of blood flow, without knowledge of the pressure in the pulmonary circuit, gives no indication of the energy expended by the right ventricle to maintain this blood flow.* We are dealing here with a mechanism somewhat similar to that of arterial hypertension of the larger circuit[5].

With an embarrassment of the right ventricle which, depending on numerous factors, may occur at various stages of the pulmonary circulatory disturbance, the peripheral venous pressure increases considerably. There is also a definite slowing of the venous blood flow. The velocity of the arterial blood is not sufficiently known at present. However, certain studies indicate that it is slower in congestive failure[24]. Considering, however, that as far as can be ascertained, the diameters of the large arteries do not show gross alterations in congestive failure; that the arterial blood pressure frequently remains unaltered; and that the blood volume and flow may be normal or lowered, one may justifiably conclude that the *slowing of the blood flow in the arterial system, if present, must be less than in the venous system.* Furthermore, as has been observed in a group of patients with advanced circulatory failure and venous congestion, the volume flow of blood to the legs may be normal and the arterial blood pressure unaltered. Thus the volume and velocity of the blood flow through the arterial system may be normal even when there is a considerable slowing in the venous system. This is substantiated by the fact that in patients whose arterial blood pressure was normal and whose venous pressure was considerably elevated up to the time of impending collapse of the circulation, post mortem examination shows a normal diameter of the aorta and large arteries but a marked increase in the diameters of the vena cava and other large veins. If during life a compensatory constriction of the arteries occurs, a rational possibility neither proved at present nor demonstrable by post mortem observations, such a mechanism would tend to maintain a normal velocity in the arterial system. The aorta could not play an active rôle in such a mechanism as it is incapable of active constriction or dilatation[25]. These considerations again bring out the following perhaps obvious, but nevertheless not fully appreciated facts concerning circulatory failure: (a) *although in a given time the total amount of blood flowing through a cross-sectional area of the larger arteries must be the same as that in the large veins; nevertheless, because of the independence and variety of the changes in the diameter of the cross-sectional areas in the venous and arterial systems, an abnormal deviation of the velocity of blood in the venous system may develop quite independently of any changes in the velocity of the arterial system;* (b) *changes in pressure in the arterial and venous systems and velocity are to a considerable extent independent.* These concepts are a rational explanation of

the fact that the arterial pressure, regardless of the degree of circulatory failure, may be normal, lowered, or slightly elevated even at a time when venous engorgement exists.

Increased venous pressure has an important effect on the capillary circulation which performs the basic tasks of the blood and circulation both in the lungs and in the periphery. As described previously, it has been repeatedly demonstrated in animals and also in man that a sensitive regulation makes it possible that an optimal capillary circulation is maintained even in the presence of a gradually increasing venous pressure. Widening of the arterioles, through nervous reflexes, chemical regulation, or elevation of the arterial blood pressure, plays a dominant rôle in maintaining this regulation. The opening of new capillaries and increased oxygen utilization are then perhaps further consequences of, rather than independent processes in, the changes that follow venous engorgement.

In the presence of severe venous engorgement the capillary pressure inevitably rises. *Thus the capillaries of the patient with congestive heart failure are always under abnormal pressure wherever the venous pressure is elevated. The velocity of the capillary blood flow is independent of the capillary pressure, and is to a certain extent determined by the functional capacity of the left ventricle.* Thus, for example, we have evidence that in hemiplegia the capillary pressure over the paralyzed side is often increased, both relatively and absolutely, with the presence of increased velocity of blood flow[62]. *The balance between the functional capacity of the left ventricle, and the velocity of the capillary blood flow on the one hand, and the degree of elevation of the capillary pressure on the other, has a fundamental relationship to cellular nutrition and function.* High capillary pressure, and a blood flow low in volume and velocity, such as occur in numerous instances of congestive failure, are a combination seriously damaging to tissue function. It produces not only a "passive congestion" and an edema *per se*—but as a result of disturbances of the internal respiration between the capillary blood and tissue cells, specific chemical substances, depending on the organs involved, appear in abnormal quantity in the blood stream. In these disturbances of tissue functions ischemia and anoxemia play important rôles, but they seldom occur without the presence of high capillary pressure and slow blood flow. Some substances, like histamine, will further specifically damage the capillary system. Others, like lactic and other acids, will increase the dyspnea through central stimulation. At this stage central chemical stimulation, in addition to the pulmonary reflexes, plays an important rôle in the production of cardiac dyspnea. Circulatory damage to the liver will completely upset the water metabolism. Circulatory changes in the kidney and other organs will break the sensitive and vital mechanism that maintains a constant acid-base equilibrium in the blood and tissues. Thus that stage of circulatory failure is now reached when the localized disease of the heart becomes a grave and extensive disease of metabolism, leading to death.

IV. Certain Applications of the Concept Presented

It has been suggested in this discussion that the simultaneous consideration of the pressure relationships in the veins, capillaries, arterioles and arteries, of the volume and velocity of blood flow, and of the permeability of the capillary system in the pulmonary and peripheral circulation together with the oxygen carrying capacity of the blood and the oxygen requirement of tissue, clarifies considerably our understanding of the clinical manifestations of heart failure. The relationship between these and other bodily functions during progressive heart disease has been computed from a series of observations and studies on a large group of patients with heart disease. Yet such a schematic presentation would carry false implications unless certain reservations were made.

Obviously not every patient with heart disease will proceed through all the stages described. Observations of the types and causes of death in cardiac patients reveal that a relatively small group of patients die in the last stage of the progressive congestive failure. Death frequently occurs abruptly at earlier stages because of precipitated arrhythmias of the heart, coronary occlusions, embolism or other vascular accidents, and uremia. Pulmonary congestion predisposes to bronchopneumonia and the added burden of this or other infections, for obvious reasons, is responsible for the death of another large percentage of cases. There is, finally, a group of patients in whom apparently none of the above factors are active. These patients, although the circulatory functions are still fairly well sustained, exhibit sudden changes in clinical appearance and die within a few hours. A number develop a rapid pulse, low blood pressure, cold skin, dyspnea, abnormal vasomotor reflexes and die with clinical evidence of peripheral vasomotor collapse and shock. One wonders whether in such instances the long persisting dyspnea, cardiac pain, rapid heart rate and other factors subject the central nervous system to an abnormal bombardment, thus causing death through a failure of the vasomotor and perhaps other nerve centers rather than through extreme congestive circulatory failure.

In applying this concept of circulatory failure to different types of heart disease the *time element* and the *nature of the cardiac lesion* should always be considered. A few examples of this will be briefly outlined, as these factors with the physiological principles presented will clarify the variations in the clinical course of circulatory failure in different types of heart disease. In the *mitral stenosis* of rheumatic fever the disturbance in the pulmonary circuit develops rather slowly and hence the right ventricle is considerably embarrassed when the pulmonary engorgement reaches a severe level. The simultaneous failure of the right side of the heart at this stage reduces the pulmonary pressure. There is thus a fairly definite relation between the pulmonary and peripheral congestion. In *arterial hypertension and aortic insufficiency,* on the other hand, an appreciable rise of pressure in the pulmonary vein occurs relatively late and only when there is a failure of the left ventricle. Hence

the engorgement and disturbance in the pulmonary circuit develop rapidly and at a period when the right ventricle has still a normal functional capacity. For this reason, evidence of pulmonary circulatory embarrassment with congestion, dyspnea, orthopnea and right hydrothorax are observed frequently in these patients in conjunction with fairly normal peripheral circulation. The same consideration bears closely on the occurrence of paroxysmal dyspnea with or without bronchial asthma early in this type of circulatory failure; and also explains a frequent clinical observation that with the onset of failure of the peripheral circulation these paroxysms frequently disappear. The onset of failure of the right side of the heart prevents the maximal elevation of the capillary pressure in the lungs and shunts a part of the blood into the periphery. As a result, the disproportion between the pressure in the pulmonary and peripheral circulation decreases and, for this reason, the patient improves subjectively and the dyspnea and orthopnea often become less. Also the state of the circulation is less favorable to the development of asthma and of right hydrothorax.

Not infrequently with the development of dependent edema and ascites, the hydrothorax disappears. Recently we observed, in the few instances studied, that with the onset of edema and ascites the velocity of blood flow through the pulmonary circuit increased and subjectively the patient felt better[28].

In accordance with the concept, it is obvious why a patient with pure *tricuspid insufficiency* may be less incapacitated with a higher venous pressure and more cyanosis than a patient with circulatory failure due to syphilitic aortic insufficiency. The pulmonary embarrassment in this condition is less, and although the venous pressure is high, the volume flow and velocity may be fairly well maintained, due to the fact that the left ventricle is efficient.

In the circulatory failure associated with preponderant embarrassment of the right or left ventricle, such as occurs in rheumatic, syphilitic and hypertensive heart disease, the disturbances in the circulation, for reasons discussed above, occur more in one portion of the vascular bed than in others. In the myocardial failure which accompanies *aging* there appears clinically a fairly *parallel failure* of both ventricles and thus the disturbances in the pulmonary and peripheral circulation tend also to be parallel. Since aging processes impair the reserve functions of all organs, including the brain, the efforts of senile patients are not apt to be out of proportion to the functional capacity of the heart. These are probably the chief reasons why a number of old people exhibit a considerable restriction in functional capacity without a clinical picture of marked congestive failure. Thus "dry failure" is not necessarily the expression of a better circulatory efficiency than congestive failure. Naturally, if through aging processes the blood supply of one ventricle, especially of the left, is more impaired than the other, the development of one or the other type of congestive circulatory failure occurs.

The prognostic significance of individual symptoms and signs of circulatory failure can be estimated only if the underlying mechanism is understood. Dyspnea, hydrothorax, cyanosis, edema and other manifestations may result from various combinations of factors and therefore the same symptom in different patients or in the same patient at different times may have a varying significance. Another reason why a single clinical manifestation has, as mentioned before, no standard significance, is that certain extracardiac factors may play a fundamental rôle in the development of the same sign. For example, the occurrence of infection during early circulatory failure may damage the peripheral arterioles, thus leading to increased capillary pressure without venous engorgement or edema. In another instance, loss of protein due to kidney damage may hasten the development of edema in a stage of circulatory failure which by itself would not produce this sign. Right hydrothorax may be the result of pulmonary engorgement, or in other instances to local pressure on the azygos vein due to aneurysm of the aorta or dilatation of the auricles or ventricles.

Numerous other specific applications of the concept may be given; but the purpose of this presentation is not a detailed analysis of the various phases, symptoms and signs of circulatory failure, but rather the interpretation of those essential clinical and laboratory observations which are of practical importance to the physician in interpreting rationally the history and physical signs of the patient. The proper use of the principles emphasized should make diagnosis, prognosis and therapy more accurate. It is hoped that investigations in progress will yield additional facts to fill out the portion of this discussion at present unsupported by observations on patients.

Summary and Conclusions

1. On the basis of a series of investigations and clinical observations on patients, a concept of progressive circulatory failure has been formulated. This concept brings into harmony hitherto uncoordinated and apparently contradictory observations. It offers a rational and more exact interpretation of the clinical manifestations of circulatory failure associated with cardiovascular diseases.

2. The interrelations between pressure, volume and velocity of blood in various portions of the pulmonary and larger circulation and in turn their relations to other bodily changes in various stages of circulatory failure are discussed. The regulatory adjustments are so complex that simultaneous measurements of several aspects of the circulation are essential to an accurate analysis of clinical symptoms and signs.

3. In the early stages of circulatory failure marked alterations occur in the pulmonary circulation, while the larger circulation is normally maintained. The elevated pulmonary venous pressure is primarily responsible for the disturbed pulmonary circulation. Recent advances in the physiology of the pulmonary circulation substantiate the concept of the beneficial regulatory functions of the pulmonary

arteriolar and capillary system. The same volume or velocity of blood flow through the lungs in various stages of failure may represent different burdens for the right ventricle and the ventilative mechanism of the lungs, and hence may be associated with varied clinical manifestations.

4. The dyspnea of early circulatory failure depends to a large extent on the altered function of the alveoli of the lung, which is secondary to changes and regulatory adjustments in the lesser circulation. These pulmonary changes set up reflexes between the lungs and the respiratory center. Chemical stimulation of the respiratory center is present only in the late stage of congestive failure of the larger circulation.

5. In failure of the larger circulation changes in pressure and velocity of blood flow may develop independently in the arteries and veins.

6. The combination of elevated capillary pressure with decreased velocity and volume flow are the chief factors responsible for damage of cell nutrition in the later stages of circulatory failure.

BIBLIOGRAPHY

[1]Eppinger, H., and Schürmeyer, A.: Ueber Kollaps und analoge Zustände, Klin. Wchnschr., 1928, vii, 777.

[2]Eppinger, H.: Ueber den postoperativen Schock, Wien. klin. Wchnschr., 1931, xliv, 65.

[3]Weiss, Soma, and Ellis, L. B.: Heart disease and peripheral circulation, Jr. Clin. Invest. (in press).

[4]Weiss, Soma, and Ellis, L. B.: Circulatory measurements in patients with rheumatic heart disease before and after the administration of digitalis, Jr. Clin. Invest., 1930, vii, 435.

[5]Weiss, Soma, and Ellis, L. B.: The quantative aspects and dynamics of the circulatory mechanism in arterial hypertension, Am. Heart Jr., 1930, 4, 448.

[6]Weiss, Soma: Unpublished observations.

[7]Blumgart, H. L., and Weiss, Soma: Clinical studies on the velocity of blood flow, IX. The pulmonary circulation time, the velocity of venous blood flow to the heart, and related aspects of the circulation in patients with cardiovascular diseases, Jr. Clin. Invest., 1928, v, 343.

[8]Hutchinson, J.: On the capacity of the lungs and the respiratory functions, with a view of establishing a precise and easy method of detecting disease by the spirometer, Med. Chir. Tr., 1846, xxix, 137.

[9]Peabody, F. W., and Wentworth, J. A.: Clinical studies of the respiration, IV. The vital capacity of the lungs and its relation to dyspnea. Arch. Int. Med., 1917, xx, 443.

[10]Binger, C. A. L.: The lung volume in heart disease, Jr. Exp. Med., 1923, xxxviii, 445.

[11]Meakins, J. C., and Christie, R. V.: Lung volume and its variations. Ann. Int. Med., 1930, iii, 423.

[12]Cohnheim, J. and Litten, M.: Ueber die Folgen der Embolie der Lungenarterien, Virchow's Arch. f. path. Anat. u. Physiol., 1875, lxv, 99.

[13]Toyama, K.: Experimentelle Forschung ueber die Lungencapillaren, Ztschr. f. d. ges. Exp. Med., 1925, xlvi, 168.

[14]Wearn, J. T.; Barr, J. S., and German, W. J.: The behavior of the arterioles and capillaries of the lungs, Proc. Soc. Exper. Biol. and Med., 1926, xxiv, 114.

[15]Hall, H. L.: A study of the pulmonary circulation by the trans-illumination method, Am. Jr. Physiol., 1925, lxxii, 446.

[16]Weiss, Soma, and Frazier, W. R.: The density of the surface capillary bed of the forearm in health, in arterial hy-

pertension, and in arteriosclerosis. Am. Heart Jr., 1930, v. 511.

[17]Wearn, J. T.: Personal communications.

[18]Lichtheim, L.: Die Störung des Lungenkreislaufs und ihre Einfluss auf den Blutdruck, 1876, August Hirschwald, Berlin.

[19]v. Basch, S. S.: Allgemeine Physiologie und Pathologie des Kreislaufs, 1892, Vienne.

[20]Blumgart, H. L., and Weiss, Soma: Clinical studies on the velocity of blood flow, X. The relation between the velocity of blood flow, the venous pressure and the vital capacity of the lungs in fifty patients with cardiovascular disease compared with similar measurements in fifty normal persons, Jr. Clin. Invest., 1928, v. 379.

[21]Ellis, L. B., and Weiss, Soma: The measurement of capillary pressure under natural conditions and after arteriolar dilatation; in normal subjects and in patients with arterial hypertension and with arteriosclerosis. Jr. Clin. Invest., 1929, viii, 47.

[22]Robb, G., and Weiss, Soma: Unpublished observations.

[23]Weiss, Soma, and Blumgart, H. L.: The effect of the digitalis bodies on the velocity of blood flow through the lungs and on other aspects of the circulation. A study of normal subjects and patients with cardiovascular disease, Jr. Clin. Invest., 1929, vii, 11.

[24]Hochrein, M., and Meier, R.: Ueber neuere Methoden zur Bestimmung der arteriellen Blutgeschwindigkeit, Münch. med. Wchnschr., 1927, 1995.

[25]Weiss, Soma: Ueber Spontankontraktionen überlebenden Arterien, Arch. f. d. ges. Physiol., 1920, clxxxi, 213.

[26]Weiss, Soma, and Ellis, L. B.: The circulatory mechanism and unilateral edema in cerebral hemiplegia, Jr. Clin. Invest., 1930, ix, 17.

Dissecting Aneurysms of the Aorta, Including the Traumatic Type: Three Case Reports*

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IN DEALING with dissecting aneurysms of the aorta one is confronted with the strange clinical paradox, that a condition which has such marked pathology is so rarely diagnosed during life. Since the lesion was first accurately described by Morgagni[1] in 1761 there have been over four hundred cases, either described or mentioned in the literature. From English and German sources, Gager[2] has collected only seven cases diagnosed during life. (See Swaine,[3] Wyss,[4] Mager,[5] Davy and Gates,[6] Moosberger,[7] Finny,[8] and Osler.[9] Etling[10] refers to five more cases all of the traumatic type, which were diagnosed before death and reports rather fully his own case of traumatic aneurysm of the aorta diagnosed while the patient was still living. (See Grant,[10a] Breton,[10b] Gils,[10c] Boyer,[10d] and Marone.[10e]) To this small group should be added a case diagnosed antemortem by Dr. E. E. Irons, which is being published. The following review contains another case which was diagnosed before death.

Although the term "dissecting" has been popularly ascribed to Laennec, it has been shown by Peacock[11] and others that M. Maunoir and Allan Burns both preceded Laennec in their use of the term.

The etiology is varied. 1. Mechanical injury, trauma from without, of special importance in the present review. 2. "Mesarteritis dessicans," first emphasized by Babes and Mironescu[12] as a disease entity and later supported by Whitman and Stein.[13] This is probably the same condition referred to by Shennan and Pirie[14] in their paper on the subject, although it is not specifically named. There seems to be a number of cases in which such a condition exists. The underlying cause of mesarteritis dessicans is not fully understood. In some cases it seems to be purely a degenerative process and in others an acute streptococcus or staphylococcus infection appears to play a rôle. The most important microscopic changes noted by the above authors are: Fatty or hyaline degeneration of the interlamellar connective tissue; thinning and rupture of the elastic fibers; atrophy of the smooth muscle. It is believed that where the underly-

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ing cause is pure degeneration, increased stress on the medial tissues because of greater distance from the lumen of the vessel, and lessened blood supply, are important factors. 3. A group of factors causing a sudden severe strain on the cardiovascular system, and presumably increased blood pressure: excitement, extreme emotional upset, heavy meals, straining and over-exertion in persons not used to great muscular effort. In practically every case of this type a generalized arteriosclerosis forms the common substratum, with such agents acting as precipitating factors. Hypertension, chronic or acute, *per se*, while not a frequent cause of dissecting aneurysm, is implicated at times. Thus Von Schnurbein[15] in an analysis of ninety-one cases found that in two, hypertension was the sole causative agent, while it was of primary importance in seventeen more. 4. Congenital. The underlying anomalies include: a, thymicolymphatic constitution with aortic and cardiac hypoplasia; b, aortic stenosis; c, dilatation of the aorta at its origin combined with a thinning of the wall. Microscopically the intima is healthy in these patients. They comprise the youngest group in whom dissecting aneurysms occur.

While it is conceded by most authorities that forces causing a sudden cardiovascular strain and increase in blood pressure do not injure the normal aortic wall of a normal individual, it is believed that such forces may precipitate a dissecting aneurysm in persons having congenital cardiovascular anomalies of the types mentioned above.

Most authorities consider syphilis as a rare cause of dissecting aneurysm. Von Schnurbein[15] found only one case in which he thought that syphilis was responsible. Further emphasis has been added by Loeschke.[16] He states that syphilis rarely if ever is the direct cause of a dissecting aneurysm, but that it may, if present in conjunction with an aneurysm of this type, aggravate the aneurysm considerably. It is true that there have been several case reports of dissecting aneurysm where syphilis was present, but the number is small enough so that the presence of syphilis might be considered coincidental. It seems probable that a luetic mesaortitis, through an interference with the blood supply leads to a degeneration of the medial fibers, and a somewhat displaced arrangement, saccular aneurysms being the sequel instead of the dissecting type.

The symptomatology has been excellently summarized by Gager.[2] The mode of onset is sudden, following excitement, exertion, or injury. The pain is outstanding, sharp and tearing, generally of higher segmental distribution than in coronary thrombosis. There may or may not be radiation. Because of the progressiveness of the pain and the disturbance of circulation in other organs, a good hint as to the diagnosis can be gained. There may be pain in the back, probably caused by a tearing of the intercostal arteries. Pain in the abdomen and groins from an interference with the abdominal arterial trunks may be present. Hemiplegia, urinary suppression, intestinal ileus, and gangrene of the

feet may follow circulatory disturbance. (See Davy and Gates,[6] Dickinson,[17] Swaine,[3] Oliver,[18] and Peabody.[19]) Severe continued pain between the shoulder blades combined with substernal pain is a rather constant finding. Findings on examination may include: a harsh rumbling bellows' sound over the aorta in the chest or abdomen; a sudden increase in the retro-manubrial dullness; adventitious swellings; and an associated inequality in the blood pressure readings and in the pulses on the two sides of the body. X-ray corroboration is important.

The diagnosis is based on a study of the symptomatology, and of the past history in an effort to discover an exciting cause. When the condition is suspected it may be necessary to make a differential diagnosis from coronary thrombosis because the type of pain is often similar in the two conditions. In dissecting aneurysm there is usually a continued cardiac competence and a lack of typical lung findings. The blood pressure generally continues at its accustomed level at least for a time, and may be unequal on the two sides of the body. With continued dissection the pain has a progressive character not found in coronary thrombosis. Electrocardiography may show only various types of irregularities. The diagnosis of this condition while the patient is still living is important, because a certain number go on to recovery. This can be aided by proper supportive measures if the aneurysm is recognized. On the other hand a wrong diagnosis may lead to an exploratory laparotomy, or some other course of treatment equally harmful.

The prognosis is grave. Crowell[20] has estimated that about 65 per cent die almost immediately from complete rupture. In another 10 to 15 per cent a sudden death usually occurs in a few days. The small number surviving this period have a good chance for recovery. In these, the aneurysm may rupture back into the aorta, or more rarely, become a closed sac filled with a clot. In both cases the false channel eventually becomes lined with intima and a "healed" aneurysm is the result, usually without sign or symptom. Obliteration of the false channel by scar tissue proliferation is extremely rare.

The intimal laceration usually occurs in that portion of the aorta which is subjected to the most strain from the constant flow of blood, namely in the origin and ascending portions. In Peacock's[11] series of eighty cases, over two-thirds showed lacerations in this region. From a prognostic point of view these are the gravest. Not only are the symptoms severe, but a great majority terminate in a short time with rupture into the pericardial sac. In general it may be said that the farther along the aorta the aneurysm occurs, the less alarming are the symptoms and the better is the prognosis for life. At the origin of the aorta and in the ascending portion and arch, the initial intimal laceration of spontaneous dissecting aneurysm is usually transverse. Elsewhere it is usually longitudinal. Practically all of the intimal lacerations of traumatic dissecting aneurysm are transverse or slightly oblique, regardless of where they are found.

Traumatic aneurysms of the aorta are practically all dissecting. While relatively more rare than the sponta-

neous type, they are being seen somewhat more frequently due to the greater number of industrial and automobile accidents occurring at the present time. About one hundred cases have been reported since 1895. War injuries have been responsible for a number. Although Hübener[21] has stated that in the case of a traumatic intimal rip which has healed without dissection there can be a saccular aneurysm formed from the stretching of the scar by the constant stress of blood pressure, it is hard to conceive that bodily reparative processes cannot, by connective tissue proliferation, reinforce such an area so that it will not become sacculated. However constantly repeated low grade traumatism may lead to a saccular formation. A case reported by McFadzean[22] showed four saccular aneurysms of the abdominal aorta and common iliacs in contrast to a relatively healthy thoracic aorta. This occurred in an old man who had for years been a trapeze and hard bar performer. There was no history of lues and no evidence of it at autopsy. In this case it was considered that the long continued traumatization of the vessels between the bar and the vertebrae or pelvic brim was the sole causative agent.

Traumatic dissecting aneurysm may occur in a healthy aorta, providing the causative force is severe enough. Indeed under certain circumstances a healthy aorta may be torn completely across. Such a case was reported by Copeland,[23] in which there was no external evidence of the cause of death. The reason for the complete rupture was not entirely clear. It could be explained by the force acting as a contre-coup. Obviously a force of less intensity is necessary to produce a traumatic dissecting aneurysm in a sclerotic and atheromatous aorta. In these cases the site of laceration seems to be the 'hyaline fibroid' lesion described by Adami,[24] which is closely attached to the media in a scar-like formation, and not the sclerotic plaque of the intima which is somewhat loosened from the media.

Traumatic dissecting aneurysm of the aorta is generally formed at the time of the accident or immediately following. It may be produced by several types of injuries. A severe blow on the chest by a large blunt force may be the causative factor. Kuhn[25] had under his care a man who was struck in the chest by a block of wood thrown from a buzz saw. A crushing injury of the chest with the fracture of several ribs, such as sustained in an auto accident or in a fall, may be responsible. (See cases below). Shennan[26] has also reported a case in which a fall caused a dissecting aneurysm. The individual struck the pavement, fracturing his clavicle and several ribs.

It has been shown that in traumatic dissecting aneurysm the initial intimal laceration is usually: (a) at or near the attachment of the obliterated ductus Botalli; (b) just above the aortic valves. It is often the posterior part of the wall that is injured. It will be remembered that the ligamentum arteriosum joins the aorta very near the root of the left lung, and is closely related to the structures of the root. This whole mass is anchored to the vertebral column by connective tissue. The aortic attachment of the ligamentum arteriosum then acts as a fixation

point. The arch as a whole is further fixed by the great arterial trunks. In the post-mortem examination of many cases, it has seemed that the hinge-like action of this attachment was responsible for localizing the point of injury. This has been emphasized by Jaffe and Sternberg[27] and Shennan.[26] The former authors found that in aviators who had fallen from various heights, there were transverse aortic lacerations at or near this attachment. The anterior wall of the aorta is not as fixed as the posterior, and the latter may be crushed against the vertebral column, thus sustaining the brunt of the impact.

With regard to the medico-legal aspect, Kauffmann[28] maintains that dissecting aneurysms do not form as the immediate effect of an accident, and that the time elapsed is generally great enough to relieve an insurance company of any responsibility. He states that a large aneurysm noticed after an accident generally speaks against any relationship between the aneurysm and the accident. On the other hand, Etling[10] has collected evidence to support the opposite view. The judgments rendered in his cases show that: 1. Traumatism is admitted to be a cause of dissecting aortic aneurysm; 2. The lesion is very serious; 3. When it occurs while at work and is so diagnosed, it may constitute the basis for damage-suits and claims for compensation; 4. Treatment should be continued over several months before an amelioration of symptoms is hoped for; 5. When symptoms persist, the lesion may be classified under the law allowing for accidents from work; 6. In point of gravity traumatic aneurysms should be placed among the causes for permanent incapacity from work.

In at least one instance[29] in this country, a Supreme Court (here of Idaho) has ruled that when a sudden strain or injury on the part of an individual during the course of employment either causes a fatal dissecting aneurysm or aggravates one already present to such an extent that the patient dies, such a fatality constitutes a death from an accidental injury and is compensible.

Case Reports

The first case is rather unusual. While not absolutely proven, it is believed that the dissecting aneurysm found at autopsy was of traumatic origin. It was undiagnosed during life, was symptomless, and played no rôle in the death of the patient. The aneurysm had occurred sometime previously, probably dating back five years to the time of the patient's rather severe injury. While it ended in a blind pocket and had not ruptured back into the aorta, the aneurysm was "healed" in the sense that it was entirely lined by endothelium and had a small blood stream functioning through a canalized thrombus which supplied the superior mesenteric and left renal arteries.

Case 1. C. W., a white man, age 73, until five years before his death had enjoyed excellent health. At that time, in the fall of 1925, he was in an automobile accident. The hospital report, furnished by Mercy Hospital, Oshkosh, Wisconsin, showed that he was admitted in an unconscious condition. General examination and x-ray, revealed an oblique fracture of the right clavicle with displacement, three transverse fractures of the sternum in fair position, and fractures of the mid-portions of the 3rd and 4th ribs on the right.

While in the hospital the patient had some blood stained sputum, but no frank hemoptysis. The first urine specimen was smoky and full of microscopic blood. Albumin and many casts were present. The blood Wassermann was negative. There was a temperature rise to at least 100° F, nearly every day. The patient was in the hospital three weeks. He was not well following discharge, but suffered considerable pain in his hips and lower spine. In Dec., 1926, he went to the Mayo Clinic. The abstracted record shows that he was suffering from a hypertrophic arthritis of the hip joints. His fractures had healed. There was some hypertension and a moderate secondary anemia. Urinalysis and blood Wassermann were negative. There was a generalized sclerosis of the pelvic vessels. No heart disease was reported. According to his daughter he had not suffered any shortness of breath or pain up to this time. Several months later he became weak and short of breath after walking against a wind. This passed off with rest. In January, 1930, his ankles began to swell and his liver became enlarged. A week of low grade abdominal pain and slight shortness of breath was followed by an attack of extreme dyspnea, and a sudden excruciating epigastric pain. This lasted some time. After a month's sickness he recovered temporarily and started to do a little work again. He did not limit himself sufficiently, and in May, 1930, he had a similar attack. He never completely recovered; and for the next five months before his admission to Presbyterian Hospital, he suffered considerably from dyspnea and dull epigastric pain. Latterly he took morphine nightly for rest and was not able to leave the house. He could lie down but rested more easily on pillows.

He was admitted in August, 1930, on the service of Dr. R. C. Brown. There was grave cardiac decompensation. The heart was enlarged, rate 60, with marked irregularity and a moderate pulse deficit. His respirations were labored and of Cheyne-Stokes' type. There were a few moist râles at the bases, the liver was enlarged and the lower extremity edema reached to the knees. There was a moderate secondary anemia. His blood chemistry was normal. The blood pressure was 168 over 102. The urine on admission showed albumin and casts, which however, cleared up before discharge. The phenolsulphonphthalein test showed a 60 per cent excretion in three hours. The electrocardiogram showed myocardial damage and ventricular extra-systoles. He was in the hospital for two and one half weeks on the usual supportive régime and showed marked clinical improvement. He remained at home for five weeks. On re-admission all his previous symptoms were aggravated. He grew gradually worse until his death ten days after admission. His rather sudden death was typically cardiac. The clinical diagnosis was: arteriosclerosis with moderate hypertension, chronic fibrous myocarditis and cardiac decompensation, and generalized anasarca.

Post-mortem Examination (*Dr. C. W. Apfelbach*). "*Anatomical Diagnosis*: Marked generalized arteriosclerosis; multiple scars of the myocardium; marked hypertrophy of the wall of the left ventricle; chronic passive hyperemia; marked anasarca of the lower extremities; ascites and bilateral hydrothorax; arteriosclerotic atrophy of the kidneys; old dissecting aneurysm (traumatic?) of the thoracic portion of the aorta.

"The aorta was opened along the dorsal wall. The scissors, cutting from above downward, entered a sac. The beginning of the sac was 14 cm. above the mouth of the celiac axis. At its upper end there was a transverse groove in the lining of the aorta about 1 mm. wide. The main channel of the aorta consisted of a narrow curved passage that admitted a thin metal ruler 1 cm. wide, the upper opening of the sac occupying at least four-fifths of a cross-section of the aorta. The narrow true passage of the aorta was on the right side of the sac. (See Figure 1*). The lower end of the main channel was at the mouth of the right renal artery, and into it also opened the intercostal arteries and the celiac axis. The sac itself was about 16 cm. long, the proximal 6 cm. being filled with fluid blood only, whereas the distal 10 cm. was occupied by canalized

*The photographs are by Mr. R. H. Leach, photographer at Rush Medical College, under the supervision of the writer.

FIG. 1. The true channel of the aorta is at the right side and the opening is held together artificially. The proximal portion of the aneurysmal sac contained only fluid blood, whereas the distal portion, where it bulged slightly, is filled by a canalized thrombus. In the true channel of the aorta the mouth of the right renal artery is visible immediately adjoining the wall of the aneurysm near the distal end of the sac.

brown dry thrombus. The lining of the first part of the sac and of the rest of the aorta had the same color but in the former region there were no sclerotic plaques or fatty deposits, both of which were abundant elsewhere.

"The superior mesenteric and left renal arteries emptied into the aneurysm through the thrombus. The front wall of the aorta bulged on the left side for a distance of about 8 cm., and this was in the region of the brown thrombus.

"The transverse groove at the beginning of the aneurysm (see Figure 2) was slightly jagged and surrounding almost all of the aorta. At the opening of the aneurysm there was a thin ridge of tissue extending across a part of the right side.

"A cross-section through the aneurysm and the main channel of the aorta (see Figure 3) in its upper third, at about the level of the sixth intercostal branch, reveals a splitting of the media of the aorta into two parts, thus making up the wall of the aneurysm. The false channel is on the right. The same relations are illustrated in a cross-section (see Figure 4) through the lower third of the aneurysm showing on the right the canalized thrombus through which the blood stream supplying the superior mesenteric and left renal arteries was maintained."

Histology. In sections of the aorta proximal to the aneurysm, stained with hematoxylin and eosin, the sub-intimal layers are moderately thickened by hyalinized fibrous tissue. The nuclei are sparse and there are a few lime salt deposits. In sections stained with phosphotungstic-hematoxylin, the elastic fibers of the media are segmented. The adventitia is not changed in any noteworthy way.

In sections through the transverse groove at the beginning of the aneurysm, the connective tissue of the intima is sparse. The scar of the depression extends through about two-thirds of the media. There are small thin-walled blood vessels scattered along the original medial tear, being more numerous here than elsewhere. There is no hemosiderin pigmentation. Distal to the scar, elastic tissue is small in amount.

In longitudinal sections through the partition separating the aorta from the aneurysmal cavity, the wall is split into two unequal parts, the greater thickness being toward the aortic side. Nuclei are few in number and all tissues stain lightly. There is an intimal lime salt deposit on the aortic side of the wall only. Extending through the middle of the section is a layer of smooth muscle fibers. The unequal split is through this layer. There are a few broken elastic fibers on the aneurysmal side of the partition.

In cross-sections through the junction of the outer wall and the partition taken about 5 cm. below the opening of the aneurysm, the media is of normal thickness on the aortic side. At the lateral edge of the aneurysm there is a split in the media, about one-third running in the wall of the aneurysm and about two-thirds running out into the partition. There is a reduplication of the partition wall. On the aortic side of the split are lime salt deposits.

In similar cross-sections taken just above the termination of the false channel, the wall of the aneurysm contains very few smooth muscle fibers, and there is a corresponding increase in the thickness of the smooth muscle coat in the partition. The dissection at this level, as judged by the small amount of involuntary muscle remaining, was very near the junction of the media and adventitia. In place of the smooth muscle fibers there is an intermediate zone in the wall of the aneurysm showing round cell infiltration and active fibroblastic proliferation. This is in the region which showed gross anterior bulging of the aneurysmal wall. Lime salt deposits are extensive. Elastic fibers are sparse.

In a few sections there is a small amount of perivascular round cell infiltration, limited to the adventitia. *Treponema pallidum* is not found in sections stained according to the method of Levaditi.

The following reasons are given as strongly suggestive of a traumatic origin for the dissecting aneurysm. The patient had a crushing injury of the chest five years before death. At no time before or since, as far as can be determined by history and communica-

FIG. 2. Illustration of the transverse scar and the ridge of tissue stretching across part of the opening of the aneurysm. The lining of the first part of the aneurysm is irregular, but there are no fatty changes like those in the wall of the upper portion of the aorta or of the true passage.

tion with the daughter, did he have any symptoms indicative of a spontaneous dissecting aneurysm of the size found, in which there must have been a temporary but serious interference with the blood supply to the left kidney and small loops of bowel. Immediately following the accident the patient had a smoky hematuria, probably from the kidney. Hanser[30] has emphasized dissecting aneurysm as a cause of blood in the urine, of renal origin. The train of symptoms and the cardiac failure responsible for his death are explainable on the basis of the coronary thrombosis found at autopsy. The original intimal laceration was in the upper part of the descending thoracic aorta and was transverse. If the aneurysm had been present previously, it would have in all probability ruptured through at the time of the accident. There was no blood staining of the tissues in the neighborhood of the scar either microscopically or macroscopically. Under similar circumstances, if the individual in question had been younger and without atherosclerosis, the diagnosis of *traumatic* dissecting aneurysm would have been unquestioned.

Case 2. This case was also believed, from rather positive clinical and x-ray evidence, to have been one of traumatic dissecting aortic aneurysm, and was so diagnosed during life. There was no post-mortem proof however. *History.* Dr. R. A. W., age 62, was admitted to the Presbyterian Hospital on the service of Dr. James B. Herrick in July, 1922. He complained of tachycardia, dyspnea on exertion, orthopnea, and swelling of the ankles.

Eleven years before at the age of 51, when previously perfectly well, he had fallen on his back from a height of ten feet. He was severely shaken up and following the fall he had hemoptysis for three weeks. During this time he suffered from a severe substernal pain and sense of oppression. The pain went through to his back. Later it became constant and aching.

A year after the accident he had his first attack of tachycardia, weakness and dyspnea, coming on suddenly while operating. Fluoroscopy showed a slightly dilated pulsating aorta. Two years after the accident x-ray showed a definite fusiform aneurysm

Fig. 3. This photograph is of a transverse section through the aorta at the upper end of the aneurysm, the false channel being on the right side. The media can be traced through most of the wall.

of the descending thoracic aorta. There was no history of lues and repeated Wassermann examinations were negative. Three years after the accident the patient had a similar attack, again while operating. Between attacks he was symptom free. During the seven years previous to his admission to Presbyterian Hospital, he had attacks of tachycardia, coming on about once a month, generally without exertion. His blood pressure averaged about 160 over 100. There was a slight albuminuria discovered nine years before.

The patient had been able to work until May, 1922, in spite of his attacks, but at that time he had a particularly bad spell, associated with a dilated heart. He rested during the four months previous to his admission, but in spite of this there was a progressive increase in the severity of his symptoms.

On admission, general examination showed a somewhat enlarged heart, and an increase in the retromanubrial dullness. No murmurs were heard. There was a systolic retraction of the precordial interspaces. The liver was enlarged but there was no ascites. Some edema of the legs was present. Urinalysis showed albumin and casts. X-ray showed a fusiform dilatation of the descending thoracic aorta.

While in the hospital there was a progressive improvement, and the patient was discharged with a diagnosis of "healed" traumatic dissecting aneurysm of the descending thoracic aorta, adhesive pericarditis

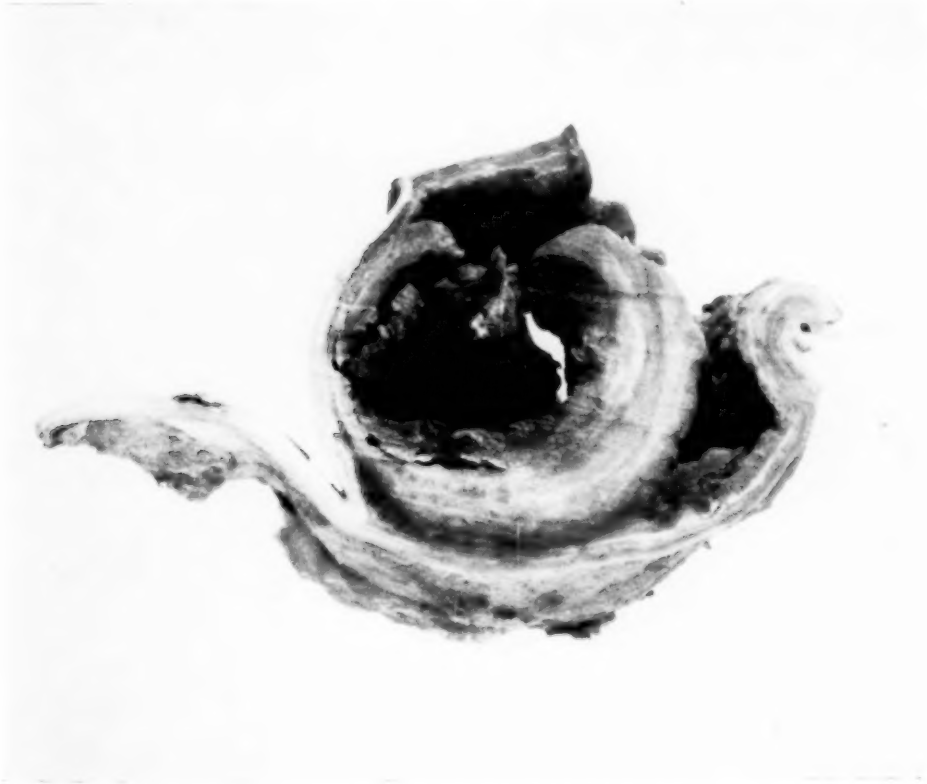

FIG. 4. This is a transverse section through the distal third of the aneurysm illustrating the canalization of the large thrombus which occupies the false channel, and the splitting of the media to form the wall of the aneurysm. The aortic channel is on the left.

and pleuritis, chronic myocarditis with broken compensation, and chronic nephritis. The patient lived some time after discharge from the hospital.

CASE 3. Through Dr. E. R. LeCount it was learned that Dr. Roger T. Vaughan, Night Warden at Cook County Hospital, had diagnosed a case of spontaneous dissecting aneurysm of the aorta during life. Aside from the obvious interest attached to a rare diagnosis, this case is important because it illustrates, also, the all too frequent tendency to diagnose a perforated ulcer because of acute upper abdominal pain.

Case Summary. J. H., a white male, age 49, was admitted to Cook County Hospital in December, 1921, at 6 P.M., after having been seen at home and sent in as a suspected case of perforated gastric ulcer. Previous to this time there had been trouble referable to the gastro-intestinal tract. However he had complained of palpitation on climbing stairs for about two months. Six weeks before the onset he had been treated at the Rush Dispensary for "heart trouble."

About five hours before admission and shortly after eating, he was suddenly seized with an agonizing knife-like pain, located principally in the epigastrium. It was constant, but waxed and waned in intensity. It doubled him up and he was very restless, rolling from side to side. The pain was something entirely new to him. He vomited several times during the afternoon, but had seen no blood. He was dizzy and covered with perspiration. Earlier, his distress had been aggravated by drinking hot water. On admission there was slight upper abdominal rigidity and moderate tenderness, localized chiefly in the epigastrium. The pain was entirely out of proportion to these findings, however. There was no fever. The pulse was 82, and of fair quality. It was palpated better in the left arm than in the right. The blood pressures were unequal, being 60 systolic and diastolic unobtained in the right arm and 115 over 60 in the left. The patient was somewhat pale. A blood count showed a leucocytosis of 12,000. There was a slight increase in the precordial dullness. The tones were rather distant and an occasional extra-systole was heard. There were no murmurs, but a rough to and fro pericardial friction rub was audible over the entire precordium. There was a retraction of the apical interspaces in systole. The lung examination was negative. On careful questioning it was elicited that the patient also had pain over the lower two or three ribs on both sides, radiating from back to front.

The conclusion drawn was that this was not a surgical abdominal condition. The absence of marked rigidity, tenderness, distension, and mass and the presence of practically normal peristaltic sounds failed to form the basis of any evidence of an intra-abdominal lesion.

The primary findings were: Severe pain in the epigastrium and lower chest, neuralgiform in character, sudden in onset, and lasting more or less constantly over a period of five hours; unequal pulses and unequal blood pressures. Along with the slight anemia this suggested a sudden accident in the chest. At his age the rupture of an aneurysm was the most likely possibility, and the relative slowness of a fatal termination suggested an aneurysm of the dissecting variety. There was no evidence of perforation into the peritoneal or pleural cavities. No aneurysmal findings such as bruit or pulsation were present. It was suspected then that the lesion was an aneurysm of the arteriosclerotic type, affecting the thoracic aorta. The patient's sudden death fourteen hours after admission with gasping, imperceptible pulse, cyanosis and syncope, was also strong evidence in favor of the suspected cardiovascular lesion. There was a questionable previous history of lues.

It is probable that x-ray examination would have made the diagnosis very easy, but the patient's condition on ad-

mission prohibited such a procedure. In addition it was felt that the diagnosis was sufficiently secure on clinical grounds alone. Post-mortem examination was confirmatory.

Anatomic Diagnosis (Dr. E. R. LeCount). "Fresh dissecting aneurysm of the aorta, innominate and right common carotid arteries; perforation into the pericardial sac; marked hemopericardium; slight left hemothorax; slight hemoperitoneum; slight hemorrhage into the tissues back of the aorta and around the innominate artery and vein; compressed right auricle and ventricle; edema and anemia of the lungs; edema and marked hyperemia of the liver; passive hyperemia of the kidneys and spleen."

Other items in the diagnosis have no bearing on the disease under discussion.

"The pericardial sac is completely filled with blood, most of which is clotted. The pulmonary artery is deeply furrowed by the pressure in front, and the right auricle and ventricle are partially collapsed. The hemorrhage has occurred from a rupture of the adventitia on the right side of the aorta. In addition to the pericardial hemorrhage, blood has seeped into the tissues just below the innominate vein and to the left of the innominate artery. There is a slightly turbid pale brown fluid in the left pleural cavity. . . . . The wall of the aorta is split all the way down to 4 cm. caudad to the renal arteries and the split extends in the other direction to the heart and is in the dorsal part of the wall. The wall of the abdominal aorta is thin, and occupying nearly all of the lining of this part, as well as of the common iliacs, are yellowish thickenings without lime. The dissection is continued into the innominate and right common carotid arteries, but these are the only branches so involved. The split in the innominate artery extends into the right common carotid artery for about 2 cm. distal to the mouth, and here there is a transverse slit in the wall about 7 mm. long, through which the lumen of the artery communicates with the aneurysm."

Summary

1. In the foregoing review we have summarized what appear to be the most important features of dissecting aneurysm of the aorta, from a clinical and pathological standpoint.

2. The etiology, symptomatology, diagnosis, prognosis and pathology of dissecting aneurysm of the aorta are given.

3. Particular stress is laid upon traumatism as an etiologic agent, with a discussion of the probable relationships of the different mechanical and anatomic factors concerned.

4. Various medicolegal aspects of traumatic dissecting aneurysm of the aorta are presented.

5. Three new cases are reported, two of which were confirmed at autopsy.

Case 1, illustrated, was probably of traumatic origin. Case 2, probably also of traumatic origin, was diagnosed before death. There was no post-mortem examination. Case 3 was a proven case of spontaneous dissecting aneurysm of the aorta, diagnosed before death.

I am indebted to the following men for timely suggestions, and for permission to use material: Dr. James B. Herrick; Dr. E. R. LeCount; Dr. C. W. Apfelbach; Dr. R. C. Brown; Dr. Roger T. Vaughan. Case records and abstracts were kindly furnished by Presbyterian Hospital, Chicago; Cook County Hospital, Chicago; Mercy Hospital, Oshkosh, Wisc.; The Mayo Clinic, Rochester, Minn.

REFERENCES

[1]Morgagni: De Sedibus, 1761. (Quoted by Gager).

[2]Gager, L. T.: Ann. Int. Med., 1928-29, ii, 658.

[3]Swaine: Trans. Path. Soc. London, 1856, vii, 106.

[4]Wyss, O.: Arch. der Heilk., 1869, x, 490.

[5]Mager: Ztschr. f. Heilk., 1903, xxiv, 323.

[6]Davy and Gates: Brit. Med. Jour., 1922, i, 471.

[7]Moosberger: Sweiz. Med. Wchnschr., 1924, liv, 325.

[8]Finny: Lancet, 1885, ii, 69.

[9]Osler: Mod. Med., Phila., 1908, iv, 468.

[10]Etling, R.: Thèse pour Doctorat en Médecine, Paris Thèses, 1904-05, No. 98.

[10a]Grant: Austral. Med. Jr., 1888, x, 393.

[10b]Breton: Arch. de Med. et Pharm. Mil., 1891, xviii, 58.

[10c]Gils: Loc. cit., 1893, xxii, 122.

[10d]Boyer: Lyon Med., July 10, 1904.

[10e]Marone: Riforma Med., 1897, 1, 386.

[11]Peacock, Trans. Path. Soc. London, 1862-63, xiv, 87.

[12]Babes, V. and Mironescu, Th.: Beitr. z. path. Anat., 1910, xlvii, 221.

[13]Whitman and Stein, J.: Jr. Med. Research, 1923-24, xliv, 579.

[14]Shennan, T., and Pirie, J. H.: Brit. Med. Jr., 1912, i, 1287 .

[15]Von Schnurbein: Frankf. Ztschr. f. Path., 1926, xxxiv, 532.

[16]Loeschke, A.: Frank. Ztschr. f. Path., 1928, xxxvi, 56.

[17]Dickinson: Trans. Path. Soc. London, 1862, xiii, 48.

[18]Oliver: Lancet, 1892, i, 1068.

[19]Peabody: Med. Record, N. Y., 1880, xviii, 326.

[20]Crowell, P. D.: Jr. Am. Med. Assoc., 1921, lxxvii, 2114.

[21]Hübener: Monatsschr. f. Unfallh. 1928, xxxv, 342.

[22]McFadzean, J.: Brit. Med. Jr., 1928, ii, 154.

[23]Copeland, G. G.: Jr. Am. Med. Assoc., 1914, lxiii, 1950.

[24]Adami, J. G.: Mont. Med. Jr.: 1895, xxiv, 945; 1896, xxv, 23.

[25]Kuhn, L. P.: Ill. Med. Jr., 1925, xlvii, 420.

[26]Shennan, T.: Jr. Path. and Bact., 1929, xxxii, 795.

[27]Jaffé, R. H., and Sternberg: Vrtljschr. f. gerichtl. Med., 1919, lviii, 74.

[28]Kauffmann: Monatsschr. f. Unfallh., 1929, xxxvi, 182.

[29]Larson v. Blackwell Lumber Co. (Idaho 279, 1087), from Jr. Am. Med. Assoc., 1930, xciv, 1529.

[30]Hanser, A., Deutsch. Arch. f. klin. Med., 1926, clii, 61.

Clinical and Experimental Observations on the Treatment of Pernicious Anemia with Desiccated Stomach and with Liver Extract*†

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Introduction

THE possibility that a defect in the stomach may be related to the etiology of pernicious anemia has been recognized for many years. This belief has been based upon a number of clinical facts, some of which have been established and confirmed by numerous observers. The most significant evidence suggesting this etiological relationship is that every patient, probably without exception, has at least a functional impairment of the stomach mucosa as indicated by the inability to secrete hydrochloric acid. This fact becomes even more significant now that it is known that hydrochloric acid is not secreted under the powerful stimulus of histamin injections, that the achlorhydria precedes all other known evidence of the disease, and that the acid does not appear in the gastric contents during a spontaneous or therapeutically induced remission. Evidence of an impaired function of the stomach mucosa, therefore, is the earliest, the most constant, and the most persistent abnormality known to exist in a patient with the disease.

Additional suggestive data pointing to the rôle of the stomach in the causation of the disease, are to be found in the reported cases of patients who have had a total gastrectomy and who later developed the blood picture of pernicious anemia. This important evidence is based upon only rare observations, as the operation usually is performed for extensive carcinoma of the stomach, recurrences of the growth may confuse definite conclusions, and many patients do not survive a sufficient period of time to permit the development of the anemia.

Opinions concerning the importance of the stomach in the etiology of pernicious anemia have been based solely upon clinical observations until recently when Castle[1] reported his classical experiments, which appear to demonstrate conclusively that there is fundamental relationship between the anemia and a defect in the gastric secretion. This observer fed proteins in the form of 300 grams of slightly cooked Hamburg steak to normal persons and recovered it after it had been

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subjected to gastric digestion for three-quarters to one hour. This material when introduced daily into the stomach of a patient with pernicious anemia, by means of a tube, promptly produced a remission in a manner similar to that following the administration of liver. From these repeated and well controlled experiments it is possible to conclude definitely that the gastric secretion of a patient with pernicious anemia is defective, as it is unable to liberate from protein a substance which prevents the development of pernicious anemia. Further work suggests that the significant defect of the gastric secretion is not the absence of hydrochloric acid, pepsin or rennin, but probably of an unknown enzyme with the capacity to liberate a product from protein, possibly a nitrogenous base, which has the ability to control the maturation of red blood cells in the bone marrow. All observations point to the cause of the anemia of pernicious anemia as a failure of the red blood cells to develop at the proper rate of speed. This must eventually result in an anemia, as a sufficient number of mature cells are not released in the peripheral blood to compensate for the red blood cell destruction which proceeds at a normal, or possibly an increased rate. It appears rational to conclude, therefore, that the reduced red blood cell production is due to an absence or diminution of this unknown substance which is normally elaborated by the secretions from the gastric mucosa acting on protein.

From the clinical observations and experiments which have been enumerated, the authors[2, 3] reasoned that the administration of desiccated normal stomach should have the capacity to remedy the fundamental defect in pernicious anemia either by supplying a sufficient amount of effective preformed material, or possibly by introducing an unknown enzyme-like substance which could liberate the effective material from protein.

Material and Methods

Since the discovery of the therapeutic value of stomach tissue in pernicious anemia, we have tested the material on over 100 patients in various stages of the disease, and reports of 232 successfully treated patients have appeared in the literature. The present report deals with the response of 50 patients whose initial red blood cell counts were below 2.9 million per cubic millimeter when treatment was begun. For two years prior to the introduction of stomach therapy, a group of patients had been treated with various types of liver extract, and fifty of these, who have been adequately treated on Lilly's Liver Extract (No. 343, N.N.R.) have been selected from our patients and the results analyzed in order to compare the effect of the two forms of treatment. Each case has been subjected to careful clinical examination, gastric analysis, blood studies, including Price-Jones measurements of the red blood cells, bilirubin estimations, and all additional studies which would make certain the diagnosis of pernicious anemia and exclude other types of anemia. In addition, each patient has shown a characteristic response to liver or stomach therapy, which lends further support to the correctness of the diagnosis. The essential information concerning

the sex, age, duration of present illness, red blood cell count prior to treatment and the dosage employed in treatment in the two groups is given in Table I.

Preparations Used and Method of Administration.—The desiccated stomach* was prepared by removing the fat and surrounding mesentery, and chopping the material very fine. This was then dried at a low temperature and the fat removed by repeatedly washing with petroleum benzine. One hundred grams of fresh stomach yielded an average of 13.3 grams (11.7 to 15.0 grams) of the dried, defatted, material. With the fat removed the material has very little odor and only a slight taste. It is not soluble in water, but may be eaten, preferably in tomato juice, as one would a thick cereal. Lilly's Liver Extract was used throughout in the second group and in most instances was given in tomato juice, but also in water or orange juice. Usually both therapeutic agents were given to the patient midway between breakfast and lunch, but occasionally the dose was divided into two equal parts by giving a mid-morning and mid-afternoon portion.

The blood studies were made at the same time each day so that comparative observations could be recorded. For the reticulocyte counts, brilliant cresyl blue-Wright's stain preparations were made, 1000 cells being counted, except when there was any doubt, in which case 2,000 or more were enumer-

*Ventriculin (N.N.R.) prepared through cooperation with Parke, Davis and Company of Detroit.

TABLE I

	Fifty patients treated with desiccated stomach—(Ventriculin)		Fifty patients treated with Lilly's Liver Extract	
Sex	Males 31	Females 19	Males 34	Females 16
Age	40 to 70 years (92%) 40 to 60 years (68%) 3 under 40 years (24, 26, 27 years) 3 over 70 years (72, 74, 74 years)		40 to 60 years (56%) 40 to 70 years (80%) 3 under 40 years (34, 35, 39 years) 5 over 70 years (72, 73, 74, 74, 75 years)	
Duration of illness	1 year or less 2 years or less 3 years or less Over 3 years	50% 62% 96% 4%	1 year or less 2 years or less 3 years or less Over 3 years	46% 62% 80% 20%
Red blood cell count before treatment	1 million or less 1.1 to 2 million 2.1 to 2.8 million	12% 58% 30%	1 million or less 1.1 to 2 million 2.1 to 2.8 million	28% 50% 22%
Dosage	80% of patients received 30 to 40 grams daily 10% of patients received 15 to 20 grams daily		68% of patients received from 5 to 12 vials* daily 18% of patients received from 3 to 4 vials daily	

*1 vial is made from 100 grams of liver.

ated. When the young red blood cells are properly stained by this method, they show a blue, fuzzy precipitate, or reticulum, in the buff colored corpuscle. The very young ones show much reticulum, whereas in those that are nearer maturity, the blue material may be confined to a few spots. If the cells are improperly stained, the entire corpuscle is grayish or bluish (diffuse basophilia) or irregularly colored (polychromatophilia). Improper staining usually results in a reticulocyte count that is low, as many of the cells are overlooked.

Effect of the Treatment on the General Condition of the Patient

Improvement in Appetite. The effect on the general condition of the patient following the administration of desiccated hog's stomach is as prompt and striking as the satisfactory change which is produced by insulin in a patient with diabetic coma, or by desiccated thyroid gland in a patient with myxedema. After the treatment has been given for from 3 to 7 days, there is a sudden and pronounced increase in appetite, which usually constitutes the earliest clinical evidence of improvement. Not infrequently the patient suddenly requests some unusual article of diet, and following this will regularly consume all of the food which is served as the ordinary hospital diet, and in many instances demand more. The development of a keen appetite within such a short time after the treatment is instituted is all the more impressive when compared to the anorexia which is often present in patients during a relapse.

Gain in Weight. As a result of the increased food intake there is usually a substantial gain in body weight. In 50 patients who were treated with desiccated stomach and in whom it was possible to obtain accurate data concerning the body weight, there was an average gain of about 20 pounds in the first 19 weeks of treatment. (Figure 1). In some patients who were markedly undernourished there was a gain of almost one pound daily for the first ten days or two weeks and one patient gained a total of 63 pounds in the first year of treatment. There was not sufficient data concerning the gain in body weight in the group of patients treated with liver extract to make an exact comparison with the group treated with desiccated stomach. The general impression, however, is that the increase in body weight in the two groups is approximately the same.

Gastro-Intestinal Symptoms. Coincident with the improvement in the appetite, all of the major gastro-intestinal symptoms are readily controlled. There is usually complete relief from nausea and vomiting within a few days, even in patients in whom these symptoms have been pronounced. In a few of those with an extremely low red blood cell count and persistent vomiting, it has been necessary to introduce the desiccated stomach by means of a stomach tube. Some of the medication has been vomited but sufficient has been retained to cause the gastro-intestinal symptoms to disappear. Other common symptoms, such as diarrhea or constipation yield to stomach therapy, as the bowel movements in almost every case have become normal. Constipation and abdominal distension,

however, may persist in those patients who have advanced spinal cord changes, even though the red blood cell count becomes normal. It is possible that this may be explained by an impairment of the nervous control of the intestines. The characteristic glossitis which was present in over fifty per cent of this group of patients is usually readily controlled by the treatment. In a few patients, it has persisted in a mild degree, and occasionally there has been recurrence of the complaint after the blood has become normal.

Fever, Pulse Rate, Gain in Strength. Other striking manifestations of improvement are the disappearance of the fever and tachycardia which are so commonly present when the anemia is severe, and a rapid gain in strength and sense of well being. Even when the anemia has been severe before treatment, the patient is usually able to become ambulatory within a week or two, and in an additional six to eight weeks may resume a normal life. Some patients have returned to their former laborious occupations, which have required more than an ordinary amount of physical strength and endurance.

Skin Changes. Additional and constant evidence of improvement is a disappearance of the yellowish pallor which is present in all patients when

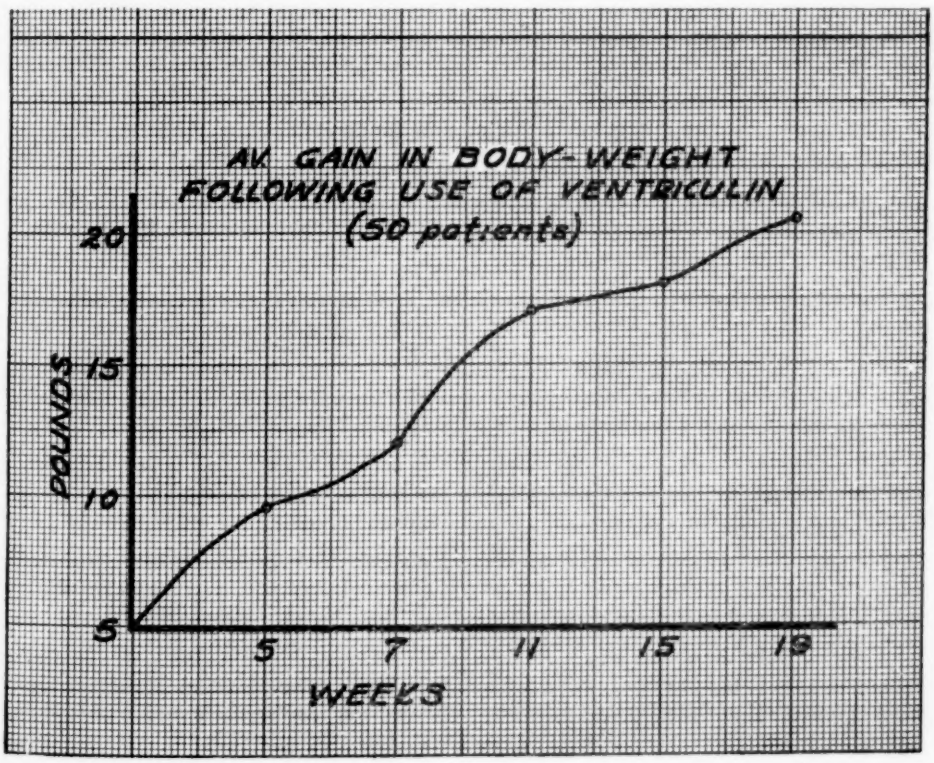

FIG. 1. Shows average gain in body weight of 50 patients treated with Ventriculin, in weeks.

the anemia is severe. This disappears as the blood bilirubin approaches normal, which is in about two or three weeks. It is interesting to note that within a few days after the treatment is begun, the pads of the fingers and palms, the chin, the cheeks and the tip of the nose become flushed. This reaction must be a vasomotor phenomenon as the flushing occurs before there is a demonstrable increase in the red blood cell count. The creases in the palms of the hands remain pale, however, and do not become red until the blood count is between 2½ and 3 million red blood cells per cubic millimeter.

Changes in the Nervous System

A very large majority of patients with pernicious anemia have symptoms referable to the nervous system of which the most common is paresthesia of the hands and feet. This symptom may entirely disappear with stomach therapy, although it is not entirely controlled in all patients. There is a less favorable effect on the more serious neurological complications, such as loss of the sense of position of the limbs, impaired control of the sphincters of the bladder and rectum, and spastic paraplegia, although occasionally the improvement may be remarkable. In some instances, the neurological manifestations are held in abeyance, or, less commonly, there may be a distinct advance in the symptoms despite the fact that the anemia has been controlled. The latter situation has not been observed so far in patients who have been treated with desiccated stomach, but has been known to occur in those who have received sufficient liver extract to keep their blood at a normal level. From our present experience, however, it is not possible to say that desiccated stomach is superior to liver in treating the neurological complications. In general it may be concluded that improvement in the minor neurological symptoms frequently occurs, but in patients with more extensive involvement, the outlook is far less promising.

Changes in the Peripheral Blood

When desiccated defatted whole stomach or liver or liver extract is fed to patients with uncomplicated pernicious anemia, a characteristic "reticulocyte response" follows. This consists of (1) a latent period, (2) a rapid increase in the absolute number and percentage of reticulocytes, reaching a maximum, followed by (3) a decrease in the percentage until the pretreatment level or slightly above (1 to 3 per cent) is reached.

Calculated Maximum Reticulocyte Per Cent

A valuable feature in studying the potency of a preparation is the height to which the reticulocyte percentage increases after the therapy has been started. Based on the study of the average maximum rise reached in many patients, Minot, Cohn and their coworkers[4] noted that there was a relationship between the maximum height of the reticulocyte count and the initial red blood cell count. The lower the red blood cell count on the day that the first dose of the medicine was given, the higher was the rise in the number of reticulocytes. Riddle's formula[5] is as follows:

$$\text{Maximum reticulocyte per cent} = \frac{0.73 - 0.2\ E^\circ}{0.73 + 0.8\ E^\circ}$$

(E° = Initial red blood cell count in millions per cu. mm.)

The following table shows the calculated maximum reticulocyte percentage with relation to the initial red blood cell count:

TABLE II

Initial Red Blood Cell Count*	Range of Maximum Reticulocyte Percentage	Average Maximum Reticulocyte Percentage
0.4	55.7 – 69.1	61.9
0.5	50.4 – 61.9	55.7
0.6	45.7 – 55.7	50.4
0.7	41.6 – 50.4	45.7
0.8	38.0 – 45.7	41.6
0.9	34.6 – 41.6	38.0
1.0	31.7 – 38.0	34.6
1.1	29.0 – 34.6	31.7
1.2	26.5 – 31.7	29.0
1.3	24.3 – 29.0	26.5
1.4	22.3 – 26.5	24.3
1.5	20.4 – 24.3	22.3
1.6	18.7 – 22.3	20.4
1.7	17.1 – 20.4	18.7
1.8	15.6 – 18.7	17.1
1.9	14.1 – 17.1	15.6
2.0	12.9 – 15.6	14.1
2.1	11.6 – 14.1	12.9
2.2	10.5 – 12.9	11.6
2.3	9.4 – 11.6	10.5
2.4	8.4 – 10.5	9.4
2.5	7.5 – 9.4	8.4
2.6	6.6 – 8.4	7.5
2.7	5.7 – 7.5	6.6
2.8	4.9 – 6.6	5.7
2.9	4.1 – 5.7	4.9
3.0	3.4 – 4.9	4.1
3.1	2.7 – 4.1	3.4
3.2	2.1 – 3.4	2.7
3.3	1.5 – 2.7	2.1
3.4	0.9 – 2.1	1.5
3.5	0.3 – 1.5	0.9

*Millions per cubic millimeter.

The average actual maximum reticulocyte per cent for the hundred patients treated by liver or stomach was 23.7. The calculated maximum for this group was 21.52 per cent. For the 50 patients treated with liver extract the actual maximum was 22.36 per cent, while the calculated maximum was 23.43 per cent. For the 50 patients treated with desiccated stomach, the observed maximum was 24.19 per cent, while the calculated maximum was 19.61 per cent.

Figure 2 shows the relationship between the observed maximum reticulocyte percentage and the initial red blood cell count compared to the calculated maximum percentage for the liver extract cases and for those treated with stomach. It is evident that the patients receiving Ventriculin made from an average of 225 grams of fresh stomach daily responded as well as, if not better than, those receiving the extract made from an average of 536 grams of fresh liver daily. If whole liver and whole stomach have the same degree of hemogenic activity, one-half of it must be lost in making the liver extract.

Of the 50 patients treated with liver extract, the average length of time required to reach the maximum reticulocyte percentage was 6.9 days, while the average for the stomach treated patients was 7.52 days, a difference of a little more than one-half day. This was exclusive of patients receiving massive doses. In view of the fact that the stomach treated patients reached, and in many cases exceeded, the calculated maximum reticulocyte percentage, the 0.62 day increase in

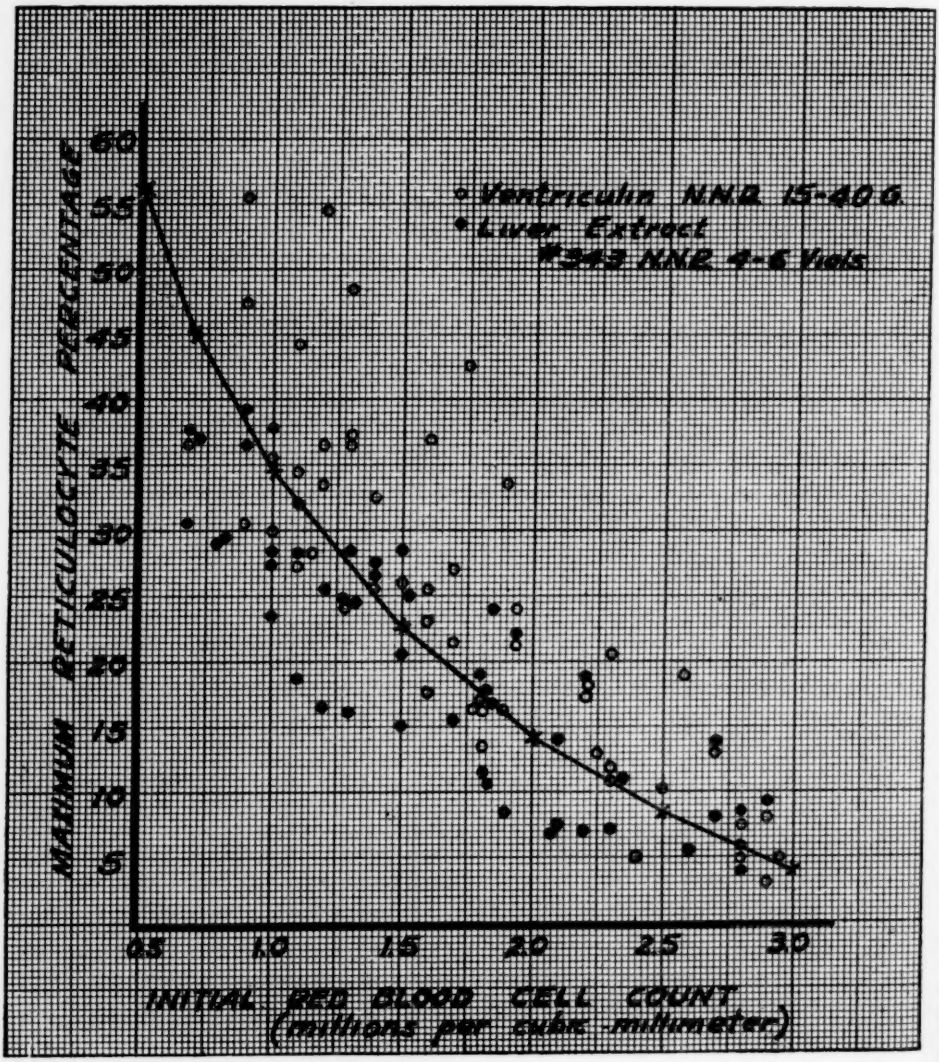

FIG. 2. The relationship between the observed maximum reticulocyte percentage and the initial red blood cell count compared to the calculated maximum percentage for the liver extract cases and for those treated with stomach.

length of time to reach the maximum must be interpreted not as deficient potency, but as evidence of a longer period required to utilize and absorb the stomach tissue. The liver extract is soluble in water, whereas the stomach tissue is not. Some of the active substance produced by the stomach tissue may be generated after the dried material has been ingested. Two lines of evidence suggest that this may be a factor, although not the only one. First, in patients in whom there is retention of gastric contents, with slow absorp-

tion, the reticulocyte response is delayed or submaximal.

1. Man (No. 233076), age 67 years. There was considerable retention of food in the stomach 15 hours after the evening meal. Initial red blood cell count 1,010,000 per cu. mm., hemoglobin 24 per cent (Sahli). The patient received 30 grams of an active preparation of desiccated stomach daily. A maximum reticulocyte percentage of 13.5 was reached on the seventh day instead of the calculated 31.7 per cent. The reticulocyte percentage returned to normal on the 11th day. The red blood cell count reached 2,760,000 per cu. mm. in four weeks and 4,480,000 per cu. mm. in ten weeks.

2. Man (No. 243961), age 70 years. Food from a meal 15 hours previously was found in the stomach on gastric analysis. There was a history of similar findings during previous gastric examinations. The initial red blood cell count was 2,610,000 per cu. mm. The patient was given 80 grams of desiccated stomach daily. A maximum reticulocyte percentage of 6.8 was reached on the seventh day, although the calculated maximum percentage was 7.5 per cent, which should have been expected for less than one-half the dosage used. In four weeks the red blood cell count rose to 3,280,000 per cu. mm.

The second phenomenon which suggests that some of the active substance may be generated after the stomach tissue is ingested, is the thermolabile character of the material as compared with the relatively more thermostabile nature of the material in liver or liver extract. While the dried stomach may be exposed for hours to temperatures of around 82 degrees C., in an atmosphere of petroleum benzene, without great loss of potency, in the presence of moisture, in 30 minutes at 60 degrees practically all the hemogenic activity is destroyed. It is possible to extract some of the active principle from fresh stomach[43] or from Ventriculin[44] with water. An acid aqueous extract (pH 4.5), evaporated at 82 degrees C. proved to be ineffective in three patients who subsequently responded well to whole desiccated stomach. An extract made by a method similar to that used in preparing liver extract, except that some of the protein was precipitated by a lead solution, showed but the faintest trace of activity (observed reticulocyte response 5.6 per cent, calculated 24.3 per cent) in a patient who subsequently responded perfectly to whole desiccated stomach tissue. It is possible that the material was inactivated when heated to the temperature of 60 degrees C. Meulengracht, et al.,[6] were unable to extract the active principle from stomach, using the methods reported by Cohn[7] in the preparation of liver extract. In interpreting these experiments it must be remembered, however, that the active principle may be destroyed more easily in the environment of the normal hog stomach tissue constituents (e.g., hydrochloric acid and pepsin present) than in the liver tissue, or may be more thermolabile.

The next group of experiments throws light on the problem from another angle. It was desired to study the hemopoietic activity of the various constituents of the stomach, to note whether one part was more active than another. It was known from clinical experience that muscle tissue (meat) alone was not active in inducing a remission in pernicious anemia. Sharp[8] had postulated the theory that stomach tissue would be an active hemogenic agent because it had arisen from the same embryonic layer as the liver, al-

though Castle's[1] work has suggested a specific secretion from the stomach as an activating agent.

The mucosa and muscularis layers were carefully separated, dried and fed separately to patients with pernicious anemia. It was found that either layer was very effective in inducing the blood changes associated with a remission if the material was not heated. Thus 300 grams of fresh muscle layer dried to 64 grams caused a reticulocyte rise of 20.3 per cent (calculated rise 17.1 per cent) in a patient whose initial red blood cell count was 1.79 million per cu. mm. However, 30 gram doses (representing 230 grams of fresh muscle layer) for 10 days failed to cause a remission when the muscle tissue was dried, defatted with acetone and exposed to a maximum temperature of 65 to 82 degrees C. in the process. Similarly 64 grams of desiccated mucosa (representing 360 grams of fresh tissue) not exposed to heat, caused a maximum rise in the reticulocytes of 41.8 per cent in a patient whose expected rise was to 25.0 per cent. This confirmed the work of Wilkinson[15] and explained our inability to obtain similar results in our original experiments[2] as the importance of the temperature factor was not appreciated at the time the first experiments were performed. The glandular portion of the mucosa, desiccated at a temperature of 65 to 82 degrees but not defatted, was fed in 30 and 60 gram doses daily (representing 158 and 316 grams of fresh mucosa) to another patient whose initial red blood cell count was 1,230,000 per cu. mm. With 30 grams daily there was a reticulocyte response to 6.8 per cent instead of the expected 27.5 per cent. With 60 grams there was a secondary rise to 9.3 per cent. Subsequently this patient received whole stomach (28 grams of desiccated stomach representing 240 grams of the fresh organ) and had a very satisfactory increase of the reticulocytes to 36.6 per cent, in comparison to a calculated rise of 20.0 per cent. In four other patients who were fed this heated mucosa, three gave no reticulocyte response at all and one gave a questionable slight response.

It is of importance to recognize, however, that when the muscle layer and mucosa are ground together, and then exposed to the temperature of 65 to 82 degrees C. in the drying process, the hemopoietic activity is not destroyed. It is thought that an enzyme-like material is formed in the mucosa, and that it acts rapidly on the muscle layer at the death of the animal, so that by the time the two layers can be separated, some of the active material has been generated or has diffused through the tissues. The work of Castle suggests that this "enzyme" or generating substance is absent in the stomachs of patients with pernicious anemia. His evidence is that it is excreted by the stomach, and the present work shows that it originates from the glands of the mucosa.

Variations in Reticulocytes During Short Intervals

Porter and Irving[20] have reported that following the administration of a potent aqueous extract of liver to patients with pernicious anemia there is a variation in the percentage of reticulocytes in as short an interval as a few hours. A study of the blood of twelve

patients (six treated with liver extract and six with desiccated stomach) was made at two to four hourly intervals to obtain additional information concerning this. It was found that in both groups there was considerable variation in the absolute numbers and percentages of reticulocytes during the course of the day. Variations up to a 16.8 per cent increase in two hours have been noted after desiccated stomach therapy and a 21 per cent increase in four hours after massive doses of liver extract. There was a tendency for the reticulocyte counts to be higher in the afternoon and evening than at other times during the day, but the incidence of the highest counts for all patients fell more frequently (3:1) during the sleeping hours (8:00 P.M. to 4:00 A.M. inclusive) than during the day (8:00 A.M. to 4:00 P.M. inclusive).

Several factors enter into the prolongation or shortening of the three periods. Chronic infection prolongs the latent period, decreases the maximum percentage of reticulocytes and prolongs the period required for the return of the reticulocyte percentage to normal. The following case histories illustrate this condition:

Effect of Infection

A patient (Case No. 240147) with pernicious anemia had septic tonsils and chronic bronchitis. His initial red blood cell count was 1,120,000 per cu. mm., hemoglobin 15% (Sahli) and leucocyte count 4800 per cu. mm. He did not develop a leucocytosis at any time. His temperature during the first 27 days ranged between 99° F, and 102.5° F. (37.5° C. to 39° C.) but was normal after the 28th day. The reticulocyte count reached a maximum of only 27.4% instead of 31.7% on the 17th day instead of the 7th or 8th day, and did not return to normal until the 29th day. However, in 62 days his red blood cell count reached 6,280,000 per cu. mm. and his hemoglobin 74% (Sahli), after taking 40 to 50 grams of dried stomach daily during the first 4 weeks and 20 grams daily thereafter.

Another patient (Case No. 235661) with pernicious anemia and acute otitis media, had a temperature ranging from 99° F. to 102° F. (37.5° C. to 38.9° C.) during the first 17 days of treatment. During this time the maximum rise of the reticulocytes in response to the daily feeding with 40 grams of dried stomach, was 11.3% instead of the calculated 45.7%. On the 9th day of therapy he was given a blood transfusion. Following this there was a subsidence of the fever and improvement physically. The dried stomach was continued, and the reticulocyte percentage fluctuated from 6.2 to 11.8%. However, on the 10th day it reached a maximum of 19.5%, which was the calculated maximum for the new post-transfusion level of the red blood cells. Subsequently his red blood cell count rose to 5,310,000 per cu. mm. and his hemoglobin to 88% while taking 20 grams of the dried stomach daily. This patient did not show a leucocytosis during his infection.

Infection may cause a fall in the red blood cell count in spite of adequate therapy. Acute infection may not only prevent the rise in the reticulocyte percentage, but when once begun may cause its rapid fall. In a patient receiving liver extract, who developed erysipelas, it was noted that there was a rapid decrease in the number of reticulocytes (inhibition of production) and a failure of the red blood cell count to increase. After the infection there was a rapid recovery in the erythropoietic function.

Another circumstance which prolongs the three periods, and which prevents a maximum reticulocyte rise to its proper degree, is found when the therapeutic preparation is weak or

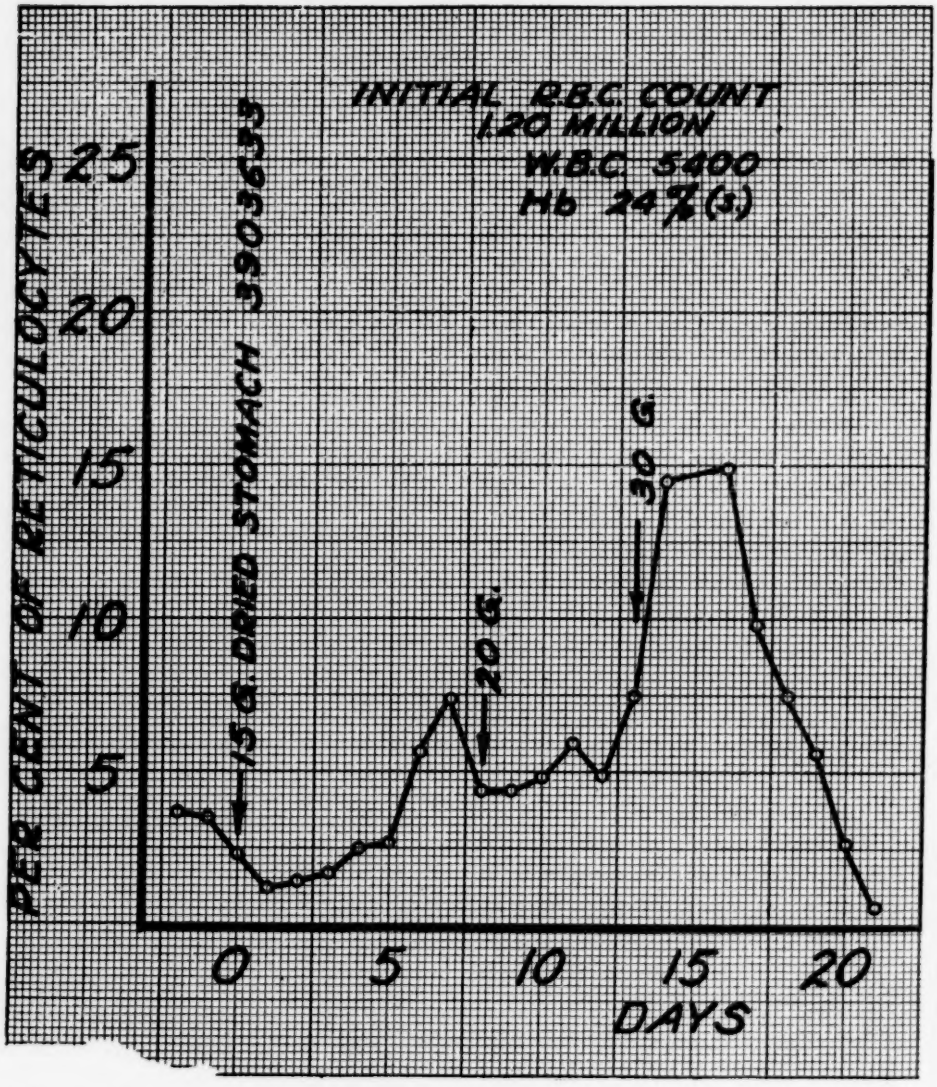

FIG. 3. Shows the effect of suboptimal doses of an experimental preparation of dried stomach of a potency lower than normal. 15 grams produced a definite effect but it was lower than one would expect. 20 grams increased the effect and the maximum response followed the increase to 30 grams daily.

when the dose is insufficient. The following figures show this condition in a patient receiving a non-defatted preparation of stomach of low therapeutic efficiency (Figure 3) and one receiving liver extract of low potency. (Figure 4).

Figure 3 shows the increasing reticulocyte response in a patient fed increasing, but suboptimal amounts, of

a special stomach preparation of low therapeutic value. Figure 4 shows the effects of two liver extracts of low therapeutic value, compared to the increase in the percentage of reticulocytes after a potent preparation.

A dose above the maximum may shorten the normal four to five day period, after therapy has begun. (Figures 5 and 6).

Patient No. 241545, age 30 years. The patient was given 50 grams of desiccated, defatted stomach on the first day, 150 grams the second day and 40 grams daily thereafter. The "reticulocyte response" began within 24 hours, and was well established in 48 hours. The maximum of 59.0% was reached on the 6th day (calculated maximum 45.7%). (Figure 5).

Patient No. 194213, age 43 years. The patient was given 30 vials of Lilly's Liver Extract by stomach tube. The "reticulocyte response" began within 48 hours, reaching a maximum of 55.7% on the 4th day (calculated maximum 45.7%). (Figure 6).

A submaximal reticulocyte rise due to a suboptimal dosage may be followed by a second reticulocyte rise if an optimal dose of an active preparation is given.

Patient No. 241529, man, age 59 years. When first examined the patient had been taking 3 vials of Lilly's Liver Extract daily for 12 days. He had an excellent subjective response, and on the 15th day his reticulocyte count had fallen to normal. He was then given 30 grams of desiccated, defatted stomach daily. A second "reticulocyte response" developed, reaching a maximum of 11.9% (calculated 20.4%).

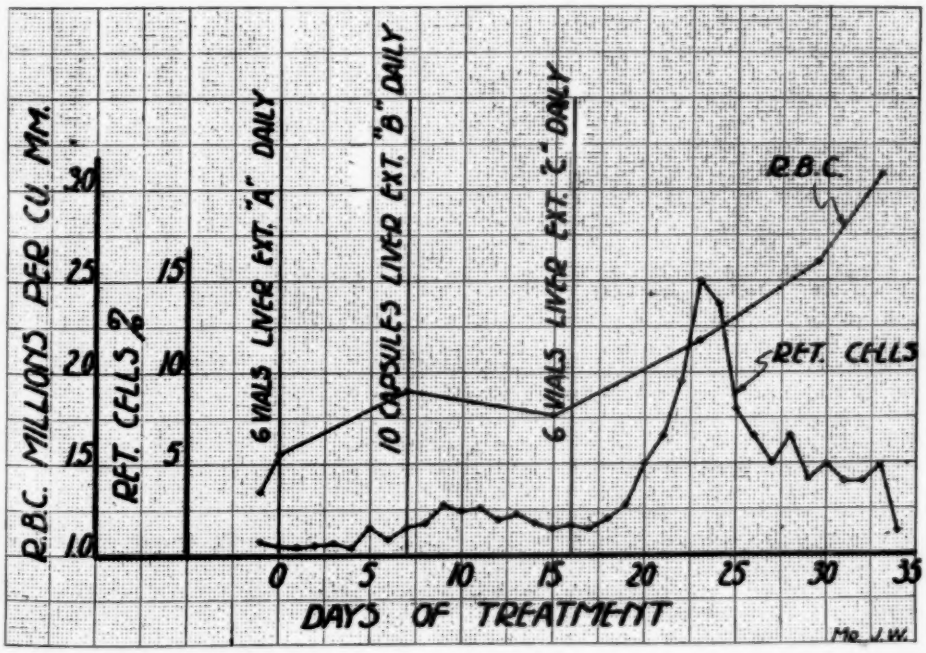

FIG. 4. Shows the effect of three commercial liver extracts on a patient with pernicious anemia. The first produced a delayed and inadequate response in increasing the percentage of reticulocytes; slightly accentuated by the second, but not at all comparable to the effect from the third. (No. 343, N.N.R.).

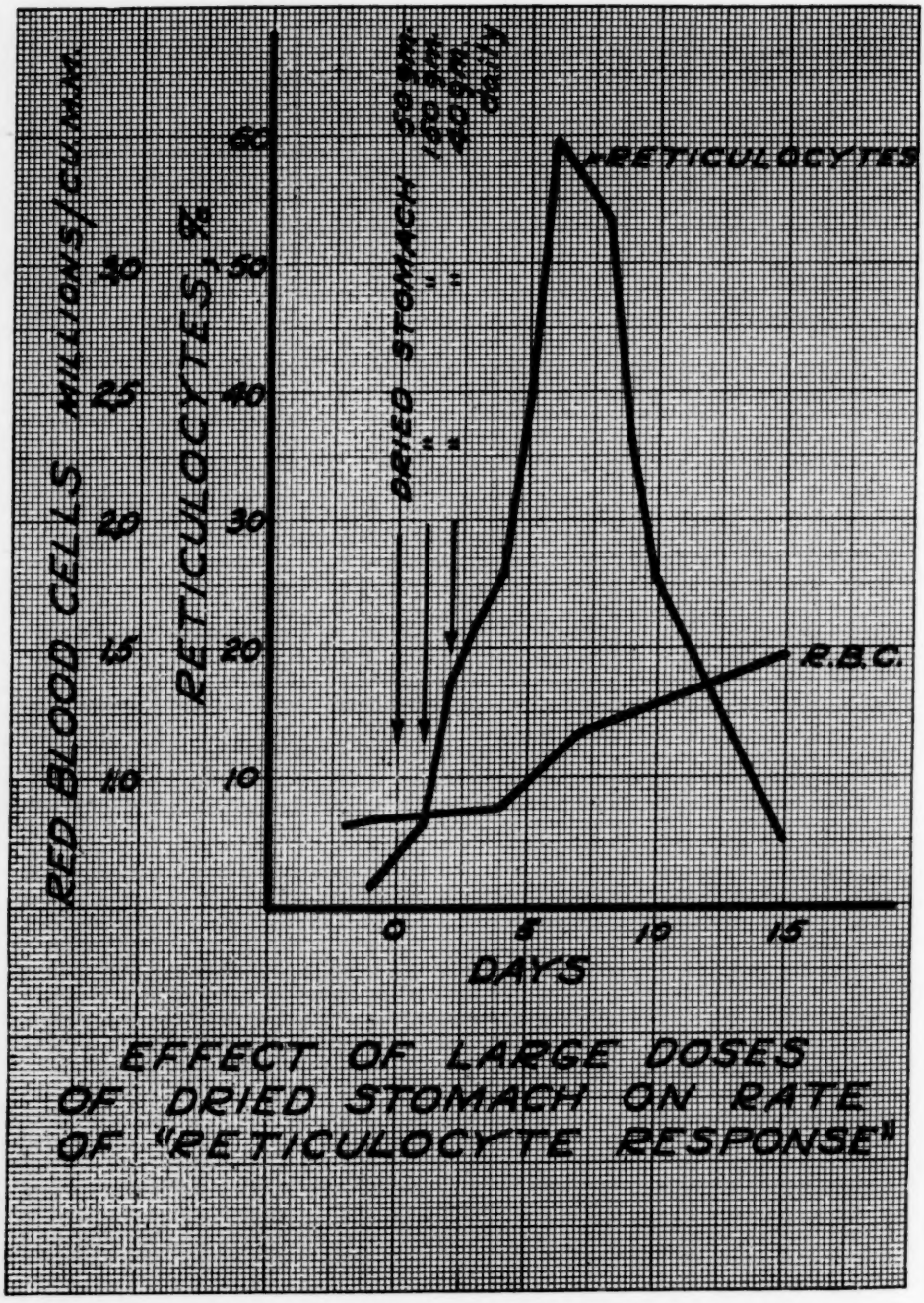

FIG. 5. Shows the rapid and marked increase in the percentage of reticulocytes after massive doses of dried stomach, given by a stomach tube, to an irrational patient with pernicious anemia. The response started within 24 hours, instead of three to five days, and reached a very high maximum.

Patient No. 227706, man, age 59 years. The patient took 3 vials of Lilly's Liver Extract daily for 21 days. At the end of this time the reticulocyte count had fallen to 7.1%, and reached normal during the next 3 days. He was then given 30 grams of desiccated, defatted stomach, and had a second "reticulocyte response" to 14.1% (calculated 38.0%).

The secondary rises in the percentage of reticulocytes are always below the calculated, the first rise having cleared out some of the immature cells of the bone marrow.

Effect of Blood Transfusion

Three patients received blood transfusions at the beginning of their dried stomach therapy, because of unusual weakness, impending infections, or exhaustion. In two of these the rise in the percentage of reticulocytes was nearer to the calculated maximum for the new, post-transfusion level of the erythrocyte number, rather than to the original pre-transfusion count. Table III).

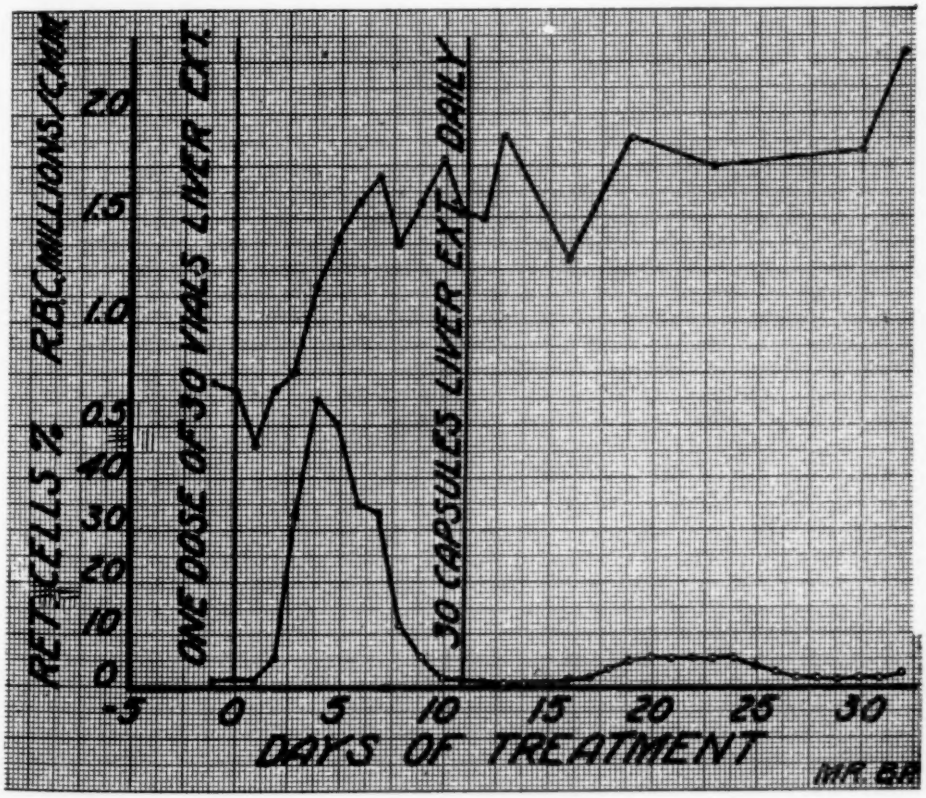

Fig. 6. Shows the rapid response when a massive dose of liver extract was fed to a patient with pernicious anemia. The reticulocyte increase began with 48 hours, instead of from three to five days.

TABLE III

Patient	Initial RBC Count Millions per cu. mm.	Expected Maximum Reticulocyte per cent.	Post Transfusion RBC Count Millions per cu. mm.	Maximum Reticulocyte per cent. Expected	Actual
241074	0.89	38.0	1.34	26.5	35.1
162296	0.69	45.7	1.21	29.0	33.5
235661	0.75	41.6	1.63	20.4	19.5

CHANGES IN THE RED BLOOD CELL COUNT

In a group of 46 of the 50 patients of whom complete data was available, the following chart shows the average increase in red blood cell count per week after adequate doses of desiccated stomach:

TABLE IV

Week	Number of Observations	Average Red Blood Cell Count Millions per cu. mm.	Week	Number of Observations	Average Red Blood Cell Count Millions per cu. mm.
0	46	1.72	7	10	4.14
1	45	1.73	8	18	4.34
2	39	2.34	9	6	4.60
3	23	2.57	10	4	4.40
4	13	3.26	11	4	4.82
5	20	3.34			
6	10	3.61			

It will be noted that during the first week of therapy there was practically no increase in the average number of red blood cells per cubic millimeter. In individual cases there was a slight increase and in others an actual decrease in number. The first significant rise is generally noted after two weeks. After the first week there is an average increase, for all the patients, of 400,000 per week. Individual patients reaching red blood cell counts of four million per cu. mm. or more showed increases of 994,000, 637,000 and 580,000 per week. The rate of increase was not equal during all months following the beginning of the treatment, being slower after the first month and comparatively very slow after the second month. Figure 7 shows the monthly changes for 46 patients, compared with those of 90 patients treated with liver diet, and reported by Minot and Murphy.[9] The average rate of increase in the two is substantially the same, being slightly more rapid in the stomach treated cases than in this liver treated group.

Relation of Size of Dose and Rate of Cell Development

There appears to be a definite correlation between the size of the dose of desiccated stomach and the time required for the red blood cell count to reach four million or more per cubic millimeter. Seven patients receiving from 100 to 199 grams per day (in terms of fresh tissue) required on the average 52.4 days to reach four million red blood cells per cu. mm. Ten patients receiving 200 to 249 grams per day required 40.1 days to reach the same level. (Figure 8). Of 25 patients with initial red blood cell counts of 0.9 to 2.8 million per cu. mm., no patient with uncomplicated pernicious anemia required more than 35 days to reach the four million level if he received more than the equivalent of 230 grams of fresh stomach, and no patient reached four million in 35 days unless he received 180 grams or more. Eleven patients in this group received from 186 to 215 grams of stomach (in terms of the fresh material) and required from 28 to 63 days to reach four million red blood cells per cu. mm., regardless of the initial count. The following table shows a comparison of the average number of days to reach the four million level when liver extract or when desiccated stomach was used. This does not take into account the varying dosage:

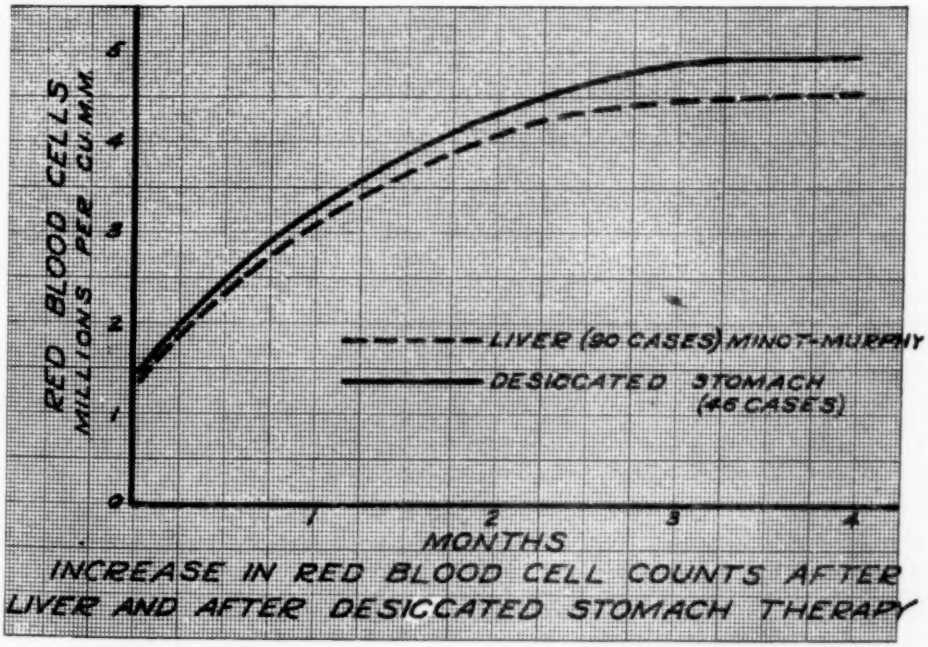

Fig. 7. Shows the average increase, by months, in the red blood cell counts of pernicious anemia patients treated with whole liver and with desiccated stomach. The upper line (stomach) shows a slightly more rapid rise when compared with the lower (liver), although the difference is probably not significant.

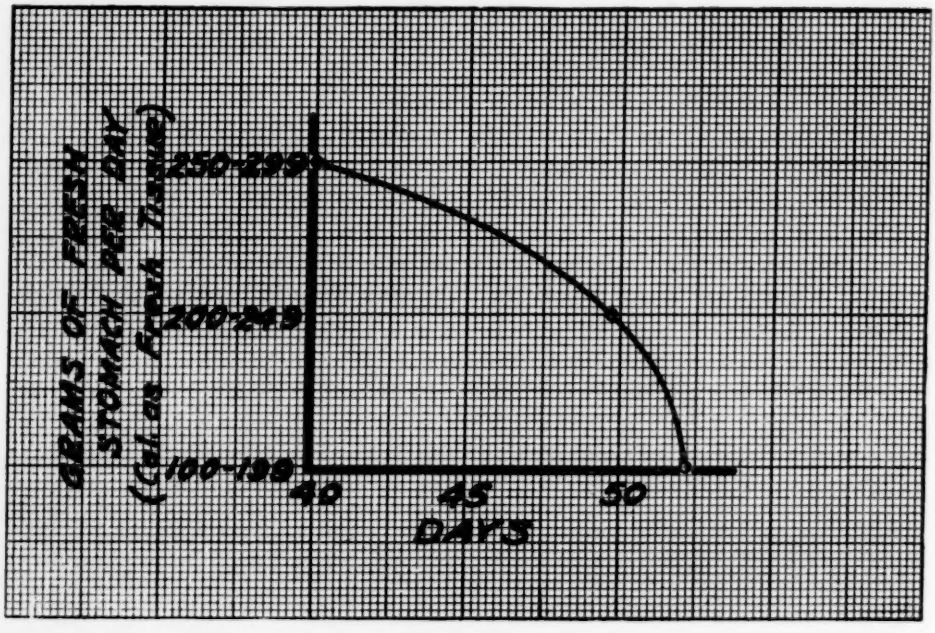

FIG. 8. Shows the average increase in the rapidity of the improvement of the red blood cell count when larger doses of desiccated stomach are fed, in comparison to smaller doses.

TABLE V

R.B.C. (Millions)	Number Patients	Liver Extract	Number Patients	Dried Stomach
0. –0.9	7	56.9 days	2	51.5 days
1.0–1.9	17	38.6 days	14	47.9 days
2.0–2.9	9	34.9 days	9	43.0 days

It is thus evident that within the dosage group classified as "adequate" it takes, on the average, comparatively longer for the patients with red blood cell counts below one million per cu. mm. to reach normal, than for those having a higher initial count. In both the stomach and liver treated groups it required but four to five days longer, on the average, for the 1.0 to 1.9 group than the 2.0 to 2.9 group to reach the four million level.

WHITE BLOOD CELLS AND PLATELETS

With the onset of the remission, there is a gradual increase in the number of white blood cells and platelets.[18] There appears to be no gross difference between the response after liver extract and after stomach therapy. Eosinophilia has been reported after raw liver diet, but no definite eosinophile increase has appeared after desiccated stomach therapy in the blood of 30 patients examined daily during the first 30 days, and at intervals during six to twelve months afterwards.[19]

RATE OF UTILIZATION, EXCRETION OR DESTRUCTION: RELAPSES

Riddle and Sturgis[10] showed that 30 vials of liver extract given in one dose had the same effect as three vials of

liver extract given daily for ten days. Kandel[21] also reported a case in which 240 grams of Ventriculin given in four days were effective for eleven days. The material is evidently stored in the body, and not excreted or destroyed at once. It is suggestive that when the material is made by gastric digestion in a normal person, it is stored, possibly in the liver, as this organ appears to have such a rich content of the material. The storage of the active material may be the mechanism by which a remission is maintained after the cessation of stomach or liver therapy. The length of a remission, when therapy is discontinued, varies with each patient. The relapse is apparently more rapid when no medication is taken than when a subminimal dose is used. Of 35 relapses in 33 patients which relapsed because of discontinuance of therapy, or too small dosage or non-potent material, records are on hand of three patients on stomach therapy and 32 on liver or liver extract therapy. The relapses, as indicated by a decrease in the red blood cell count, appeared in from ten days to nine months. The average period for the development of a complete blood relapse is probably slightly less than two months, and appears to be essentially the same in patients treated with liver extract or with stomach, although the series is at present too small to permit the drawing of definite conclusions. In the three relapses in patients treated with stomach, the blood count decrease was noted in from two to two and one-half months after a normal blood count, during which period the medication had been discontinued or an insufficient amount taken. The most rapid relapse after liver extract therapy was noted in a patient in whom the red blood cell count fell from 5,060,000 per cu. mm. to 2,300,000 in ten days. There is evidently rapid destruction or counteraction of the hemopoietic substance during infection.

Patients Apparently Refractory to Liver, Responding to Dried Stomach

Occasionally a patient is encountered who does not respond perfectly to liver, and the blood count cannot be increased appreciably above three million per cubic millimeter. The following case history illustrates this point:

A man (Case No. 210673), age 65 years, gave a history of pernicious anemia of at least 3 years duration. When liver extract, 6 vials daily, (343, N.N.R.) was begun his red blood cell count was 1,250,000 per cu. mm., and his hemoglobin 25% (Sahli). He had a typical "reticulocyte response" and in 23 days his red blood cell count was 3,400,000 per cu. mm. and his hemoglobin 65% (Sahli). He was given 4 vials of a liver extract daily after this, but no change was noted in the blood count in 36 days. It was thought that the particular liver extract used was not of normal potency, so the dose was doubled (8 vials daily). No change occurred in 21 days and the liver extract was changed to a lot of known potency, 4 vials (343, N.N.R.) daily. There was a slight drop in the red blood cell count in 30 days, it was unchanged in 35 more days of this therapy, and again the same after 34 more days, and 26 days and 63 days. Thus the blood count remained around 3 million for 245 days using what was usually an adequate dose of a potent liver extract. The patient was then given 14 grams of dried, defatted stomach daily, the dose being reduced to 10 grams later. The blood count taken 8 weeks later showed a slight increase to 3,870,000 red blood cells per cu. mm., and 83% hemoglobin (Sahli), with great subjective improvement. The count rose

rapidly to 4,390,000 per cu. mm. and the hemoglobin to 91% (Sahli) where it has remained for 3½ months to the present.

Renshaw,[11] Leschke,[23] and Snapper and Dupreez[12] reported similar cases.

Effect of Liver Extract, Liver or Desiccated Stomach on Secondary Anemias

Sixteen patients with various types of anemia were treated with liver or liver extract and three with desiccated stomach. In only two was there a therapeutic response attributable to the medication. One, a patient with fish tape worm infestation and anemia, responded well to whole liver and the other, a patient with myxedema and anemia, responded to liver extract. While either liver or stomach therapy appears to be specific for the macrocytic anemias of the pernicious anemia type, including sprue (Castellani,[13]) it is possible that empirically other conditions may be found which may be helped.

Causes of Failure in the Treatment of Pernicious Anemia with Desiccated Stomach or Liver Extract

Our experience seems to have demonstrated clearly that the blood of a patient with uncomplicated pernicious anemia will return to normal following the administration of adequate doses of desiccated hog's stomach.[2, 3] Proof of this is to be found in treating our own series of 100 patients and confirmatory evidence is available in the published results of Conner,[14] Wilkinson,[15] Renshaw,[11] Snapper and Dupreez,[12] Rosenow,[16] Meulengracht and Hecht-Johansen,[6] Hitzenberger[17] and others.[21-45]

When the treatment is applied to some patients, however, the anticipated improvement may not follow. This situation requires the careful consideration of several possible explanations as follows:

1. The diagnosis of pernicious anemia may be incorrect. As far as it is known at present, desiccated stomach is effective only in pernicious anemia and sprue.[13] Assuming that it has an action similar to liver or liver extract, it may be surmised that it will also benefit patients with the so-called "pernicious anemia'" of pregnancy, and the anemia associated with *Dibothryocephalus latus* infestation. There are other varieties of anemia which resemble the pernicious type and yet do not respond to stomach therapy. Probably one of the most confusing is aleukemic leukemia, which in some instances is differentiated from pernicious anemia only with the greatest difficulty. All other types of anemia which do not respond to the modern treatment of pernicious anemia must be eliminated before it can be said that the therapy is ineffective.

2. It is known that any type of acute infection with a febrile reaction reduces, to a certain extent, the effectiveness of desiccated stomach. If the treatment fails, therefore, an attempt should be made to eradicate all forms of active infection. If this cannot be eliminated, the dose should be doubled and every effort made to minimize the effect of the counteracting agent.

3. Occasionally failure is due to the fact that the patient is not under constant observation and takes only a small portion of the prescribed dose. Too often efficient therapy is discarded be-

cause the red blood cell count is said not to increase during the first week or two of treatment. While it is true that the average red blood cell count increases between 400,000 and 500,000 per cu. mm. per week, this increase is not always in the form of a smooth curve for each patient. As shown in an earlier section, in some there is no change for a week or two, and then a rapid rise at the rate of a million or more cells per cu. mm. per week. It should be emphasized, furthermore, that the earliest change which is noted in the blood is not necessarily a rise in the red blood cell count but an increase in the reticulocytes. It should also be emphasized that the number of reticulocytes which appear following treatment is inversely proportional to the initial red blood cell count before treatment, and that they do not show as an increased percentage in the peripheral blood when the red blood cell count is three million or more.

4. If the above possible explanations can be eliminated, it must be concluded that the preparation used is not potent. This possibility may be eliminated if the preparation which has been used is known to have been subjected to a clinical test by responsible observers and certified as active. The preparation of defatted, desiccated hog stomach is not a complicated procedure, and the possibility of destroying the potency of the material during the manufacturing process should not be great. But, as the active material in the substance is not identified, its exact stability to heat and various changes of pH are not known, and very slight alterations in these may readily impair or completely destroy the potency of the preparation.

Practical Management of Patients with Pernicious Anemia

The essential part of the treatment is to be assured that the patient receives a sufficient amount of potent material which is effective in the treatment of pernicious anemia. If desiccated stomach (Ventriculin) is used, a safe daily dosage is ten grams for each million deficit in the red blood cell count. For example, if the red blood cell count is one million, there is a deficit of four million, and the dosage should be 40 grams daily; when the level of the red blood cell reaches two million, the deficit is three million, and the dosage should be 30 grams daily. After the blood becomes normal it is necessary for the patient to continue with a maintenance dose for an indefinite period in order to prevent a relapse, which will occur at a variable period after the medication is discontinued. The precise dosage per week which is necessary to prevent a recurrence of the anemia is not definitely known at present, and it is possible that it varies with different patients. An average dosage is ten grams a day for five or six days a week. When the dosage has been reduced to ten grams daily, the only safe plan is to have the patient report at intervals of every two or three weeks for a blood examination. If the red blood cell count remains at a normal level for over two months, it may be concluded that the dosage is adequate, but if there is a decrease, a larger dosage is indicated. From our experience we have con-

cluded that the most accurate single criterion of the adequacy of the dosage is the level of the red blood cells, and this should be determined at each time the patient returns for examination. Although the red blood cell count may increase to more than five million per cu. mm., there is no evidence that it will reach an abnormally high level if an excess of medication is given. The fear, therefore, that a polycythemia may develop is unwarranted.

The accessory methods of treatment depend upon the symptoms. A patient with anemia should remain at rest in bed for the first week or two of the treatment if the red blood cell count is extremely low. It has been our practice, however, to urge patients to become ambulatory at the earliest possible moment but to avoid excessive fatigue. The diet should be liberal and well balanced, but otherwise requires no special attention. With a few exceptions, the choice of food may be left to the patient as the increased appetite which develops with the treatment usually calls for a wide variety of food in large amounts. There is no convincing evidence that it is necessary to administer dilute hydrochloric acid, despite the fact that patients with pernicious anemia have an achlorhydria and free hydrochloric acid never returns in the gastric contents after the blood becomes normal. In the series of patients whom we have treated about one-half were given dilute hydrochloric acid in doses of 4 c.c., t.i.d., or more, and the others received no medication except liver, liver extract or desiccated stomach. The results in both groups were equally good and there was no apparent difference in the rate of recovery from the anemia or the rapidity with which the gastro-intestinal symptoms disappeared. As the effect of the modern method of treatment is so prompt and satisfactory, it does not seem necessary to employ the therapeutic agents such as iron and arsenic, and they have not been used in the patients whom we have observed.

For the prevention of bed sores, reddened areas may be coated at frequent intervals with a collodion solution. When the bed sores are large, necrotic tissue may be cut away and wet dressings of boric acid can be applied. When the edges become clean, the wound may be exposed to the air, or to the light and heat from an ordinary carbon filament electric light bulb.

Importance of Complicating Infections

As previously emphasized, an acute infection of any type, if it is associated with fever, causes the action of liver or desiccated stomach to be less effective. The infection which is most frequently encountered is one involving the urinary tract, and usually consists of a cystitis alone or a cystitis associated with a pyelitis. This arises in patients with spinal cord changes, which result in urinary retention due to loss of control of the sphincter of the urinary bladder. Any other type of infection, such as acute tonsillitis, sinusitis, bronchitis, bronchopneumonia, acute cholecystitis, or erysipelas may produce the same deleterious effect. It is doubtful if various foci, such as chronic and mild infection about the teeth, are of importance in this connection, and, therefore, their removal

should be recommended only after it has been demonstrated conclusively that efficient stomach therapy is not producing satisfactory results. In the presence of an acute complicating infection with fever, every method to combat it should be employed, and in addition the dose of desiccated stomach should be increased from 50 to 100 per cent.

Blood Transfusion

It is rarely necessary to resort to this procedure as most patients react promptly to liver or stomach therapy. It is useful, however, as an emergency measure, and should always be considered when the patient's condition is serious or if red blood cell count is one million per cu. mm. or less. It has been our practice to determine the blood group of all patients whose red blood cell count is one million or less, and to have a donor available for use if it appears that the patient may die before the usual therapy has time to act. Some patients with an extremely low red blood cell count are delirious and uncooperative when first seen, which makes impossible the administration of any medication by mouth. As there is no effective preparation of liver or stomach, commercially available which can be administered subcutaneously or intravenously, and the injection per rectum is only moderately efficient, the medication must be given by means of a stomach tube. Excellent results may be obtained by employing a tube with semi-rigid walls and administering 100 grams or more of desiccated stomach which has been mixed with a sufficient quantity of water to insure that it will pass through the tube readily. Although a portion of this may be vomited, a sufficient quantity will be retained to produce an effect, and more may be given at intervals of three or four hours.

Discussion

The fact that desiccated, defatted, hog's stomach is effective in the treatment of pernicious anemia is of importance from a practical as well as a theoretical standpoint. There is no evidence that this preparation is more effective than liver in the treatment of this disease, although our observations are compatible with the conclusion that fresh stomach tissue contains, or develops, the active substance in a more concentrated form than fresh liver. It is possible, however, that this is not the case, as a fairly large amount of the active principle in liver may be destroyed or lost in the process of manufacture of liver extract. As the preparation of desiccated stomach is relatively simple and the original tissue employed is ordinarily regarded as a waste material, the cost of the finished product should be less than liver extract. When it is considered that a patient with pernicious anemia must consume a certain amount of effective material constantly in order to maintain health, this is an important item for consideration. Most of the patients do not find the material difficult to consume, and some prefer it to liver extract. At present liver extract has the advantage of being soluble in water, whereas the desiccated stomach does not dissolve.

Certain theoretical considerations as to the nature of the development and method of action of the blood-maturing substance offer opportunity for

speculation. The blood-maturing substance appears to be present in liver tissue as a definite material and it can be extracted and concentrated. The potency of the whole stomach suggests, then, that the material is developed post mortem in the tissues. A generating substance, then, may exist in one layer (the mucosa) which acts on the proteins of the other layer (muscularis). It is possible that the generating substance is of the nature of an enzyme, and it is apparently excreted in normal gastric juice. The fact that the material can be made in the stomach during gastric digestion; and is present in liver and other tissues, leads one to conclude that it may be made and stored by the body. This probably accounts for the latent period of development of anemia when liver or desiccated stomach tissue therapy is discontinued. The desiccated stomach may have a supply of the active substance which it has generated while drying, or additional substance may be made after it has been ingested. Meulengracht and Hecht-Johansen[6] suggest that this is the case, as they were unable to extract it by the method of Cohn used in making liver extract. However, it may be that the material is destroyed by this process, although it hardly seems possible that it should be stable in liver tissue and not in stomach tissue.

The fate of the substance is not known. The quantitative relationship between the size of the dose and the rate of response, and the relapse when the dose is below a certain minimum, suggests that a certain definite amount of the material is used. More of the active substance is required and used when the peripheral blood count is low than when it is high. Three vials of Lilly's Liver Extract or ten grams of desiccated stomach (Ventriculin) daily, supply sufficient material when the red blood cell count is four and one-half to five million per cu. mm., but the response is very slow if this dosage is given when the cells number one million or less per cu. mm.

There are several possible ways in which the active material may act:

1. *Replacement Theory*: The active material may supply a missing substance directly and cause a normal development of the blood.

2. *Hormone Theory*: It may stimulate other organs, or tissues, to produce an adequate amount of a hemogenic substance, or change the rate of growth of the bone marrow cells directly.

3. *Defective Metabolism Theory*: It may act as an intermediate substance which, after undergoing further metabolic changes, becomes part of the developing red blood cells.

4. *Antitoxin Theory*: The material may neutralize an inhibiting substance.

The lessened activity of the active substance as the blood count approaches normal, as evidenced by the decreased production of reticulocytes and the slower rate of increase of the red blood cell count during the later weeks and months after the beginning of therapy, suggests that the material has a specific action on the stages of the red blood cell which are most numerous during the relapse, the megaloblast and normoblast. It is possible that the increase in the number of white blood cells with the onset of the remission is a mechanical incident, associated with the release of large num-

bers of cells from the crowded, hyperplastic bone marrow. This is somewhat substantiated by the absence of improvement in the leukemias after liver extract or desiccated stomach therapy.

Summary and Conclusions

1. Defatted, chopped, desiccated whole stomach (hog) is effective in inducing and maintaining a hemopoietic remission in pernicious anemia.

2. A comparison has been made in the clinical progress and laboratory data of 50 patients treated with Lilly's Liver Extract (No. 343, N.N.R.) and 50 patients treated with desiccated, defatted stomach (Ventriculin, N.N.R.).

3. The defective maturation of immature red blood cells in the bone marrow of patients with pernicious anemia appears to be related to the lack of an enzyme-like substance developed in the gastric mucosa.

4. The material made by the mucosa, produces from protein a substance which stimulates red blood cell maturation.

5. The material may be produced post-mortem when the mucosa and muscle layer are ground together.

6. The subjective and objective changes in both groups (liver treated and stomach treated) are alike.

7. As with liver extract, the maximum reticulocyte count is inversely proportional to the initial red blood cell count, after desiccated stomach therapy. The anticipated maximum reticulocyte count may be estimated with a remarkable degree of accuracy.

8. The reticulocyte count may vary during the course of the day from one or two per cent to 16.8 or 21.0 per cent, in two to four hour intervals. The greatest increase in the reticulocyte percentage came most frequently during the hours of sleep at night, in the cases studied.

9. The response to the therapy may be lessened or inhibited in the presence of infection or if the preparation is weak or the dose insufficient.

10. The latent period before the development of the reticulocyte increase may be shortened by a massive dose of liver extract or desiccated stomach.

11. A submaximal reticulocyte rise, due to a suboptimal dosage, may be followed by a second reticulocyte rise if an optimal dose of a second preparation is given.

12. The reticulocyte response may be submaximal in patients who have gastric retention.

13. A decrease in the maximum reticulocyte percentage following desiccated stomach therapy has been noted after blood transfusion.

14. The average length of time for 50 patients treated with Ventriculin to reach the maximum reticulocyte percentage was 7.52 days, whereas for the liver group it was 6.9 days. The difference is attributed to the greater solubility of the liver extract, with more rapid absorption.

15. The average maximum reticulocyte percentage of the liver treated group was 22.36 per cent (calculated 23.43 per cent) while that for the stomach treated group was 24.19 per cent (calculated 19.61 per cent).

16. During the first week or two of therapy the increase in the number of

red blood cells may be negligible, but after that there is an average increase of about 400,000 per week, more rapid during the early weeks and slower as the five million level is reached.

17. Within the limits of adequate dosage, the larger the dose of desiccated stomach, the shorter the time required to reach a normal red blood cell count.

18. With the development of the remission, the number of leucocytes and blood platelets approaches normal.

19. No eosinophilia has been noted after stomach therapy, as after raw liver therapy.

20. The active material in liver extract or desiccated stomach may be stored in the body, the supply or effect being adequate for a variable period, but is rapidly counteracted or neutralized by infection.

21. Causes of failure of liver extract or desiccated stomach therapy are incorrect diagnosis, infection, insufficient dosage, or deficient potency of the preparation.

22. The optimal daily dosage of desiccated stomach is ten grams (equivalent to about 67 to 70 grams of fresh stomach) for each one million deficit in the red blood cell count.

23. Active infection must be eliminated and in its presence the dose of desiccated stomach or liver extract must be increased.

24. Blood transfusion may be indicated in selected cases with extremely low blood counts, debility or acute infection.

BIBLIOGRAPHY

[1]Castle, W. B. and Locke, E. A.: Observations on the etiologic relationship of achylia gastrica to pernicious anemia. Jr. Clin. Invest. 1928. vi, 3-4.

Castle, W. B.; Townsend, W. C., and Heath, C. W.: Etiological relationship of achylia gastrica to pernicious anemia. Lancet, 1930, i, 1062-3.

Castle, W. B.: Observations on the etiologic relationship of achylia gastrica to pernicious anemia. I. The effect of the administration to patients with pernicious anemia of the contents of the normal human stomach recovered after the ingestion of beef muscle, Am. Jr. Med. Sci., 1929, clxxviii, 748-764.

Castle, W. B., and Townsend, W. C.: Observations on the etiologic relationship of achylia gastrica to pernicious anemia. II. The effect of the administration to patients with pernicious anemia of beef muscle after incubation with normal human gastric juice, Am. Jr. Med. Sci., 1929, clxxviii, 764-777.

[2]Sturgis, Cyrus C., and Isaacs, R.: Desiccated stomach in the treatment of pernicious anemia, Jr. Am. Med. Assoc., 1929, xciii, 747-749.

[3]Isaacs, R., and Sturgis, Cyrus C.: Some newer remedies in the treatment of pernicious anemia; desiccated stomach, Jr. Am. Med. Assoc., 1930, xcv, 585-587.

[4]Minot, G. R.; Cohn, E. J.; Murphy, W. P., and Lawson, H. A.: Treatment of pernicious anemia with liver extract; Effects upon the production of immature and mature red blood cells, Am. Jr. Med. Sci., 1928, clxxv, 599.

[5]Riddle, M. C.: Blood regeneration in pernicious anemia during early remission, Arch. Int. Med., 1930, xlvi, 417-439.

[6]Meulengracht, E., and Hecht-Johansen, A.: Behandlung der Perniziösen Anämie mit Magen und Magenextrakt, Klin. Wchnschr., 1930, ix, 1162-1165. Ugesk. f. Laeger, 1930, xcii, 405-409.

[7]Cohn, E. J.; Minot, G. R.; Alles, G. A., and Salter, W. T.: The nature of the material in liver effective in pernicious anemia, II. Jr. Biol. Chem., 1928, lxxvii, 325-358.

[8]Sharp, E. A.: An antianemic factor in desiccated stomach, Jr. Am. Med. Assoc., 1929, xciii, 749.

[9]Minot, G. R., and Murphy, W. P.: A diet rich in liver in the treatment of pernicious anemia, Jr. Am. Med. Assoc., 1927, lxxxix, 759-768.

[10]Riddle, M. C., and Sturgis, Cyrus, C.: The effect of single massive doses of liver extract on patients with pernicious anemia, Am. Jr. Med. Sci., 1930, clxxx, 1-11.

[11]Renshaw, A.: Treatment of pernicious anemia with desiccated hog's stomach, Brit. Med. Jr., 1930, i, 334-335.

[12]Snapper, I., and Dupreez, J. D. G.: Behandeling von pernicieuse anaemie met Poeder von Gedroogde Varkensmagen, Nederlandsch Tijdschrift voor Geneeskunde, 1930, lxxiv, 745-747. Nederlandsch Tijdschrift voor Geneeskunde, 1931, lxxv, 29-48.

[13]Castellani, A.: Brief notes on the administration of liver, pancreas and stomach extracts in sprue, Jr. Trop. Med. and Hyg., 1930, xxxiii, 126.

[14]Conner, H. M.: The treatment of pernicious anemia with raw and cooked swine stomach, Jr. Am. Med. Assoc., 1930, xciv, 388-390. Jr. Am. Med. Assoc., 1931, xcvi, 500.

[15]Wilkinson, J. F.: Pernicious anemia; preliminary report on the results obtained by treatment with certain preparations of stomach, Brit. Med. Jr., 1930, i, 236-239.

[16]Rosenow, G.: Behandlung der perniziösen Anämie mit getrocknetem Schweinemagen, Klin. Wchnschr., Berl., 1930, ix, 652-653.

[17]Hitzenberger: Case report, Proc. Gesellsch. f. inn. Med. in Wien., Wien. klin. Wchnschr., 1930, ix, 293.

[18]Nittis, Savas: Blood platelets in pernicious anemia after liver therapy, Ann. Int. Med., 1931, iv, 931-938.

[19]Goldhamer, S. M.: Non-development of eosinophilia in pernicious anemia patients treated with desiccated stomach, Ann. Int. Med., 1931, iv, 1105-1107.

[20]Porter, Wm. B., and Irving, Hazelwood: Reticulocytosis produced by liver extract, Arch. Int. Med., 1929, xliv, 502-503.

[21]Kandel, Ernestine: Ventriculin in the treatment of pernicious anemia patients on meat free diet, Proc. Soc. Exp. Biol. and Med., 1931, xxviii, 385-389.

[22]Geuting, H.: Treatment of pernicious anemia with stomopson, Deutsch. med. Wchnschr., 1930, lvi, 1219-1220.

[23]Leschke, E.: Die magentherapie leberrefraktarer Falle von perniziösen Anämie, Med. Klin., Berl., 1930, xxvi, 1445-1446.

[24]Decastello, A.: Erfahrungen über die Behandlung der perniziösen Anämie mit dem Magenpräparat Venträmon, Med. Klin., Berl., 1930, xxvi, 1444-1445.

[25]Bertram, F.: Klinisches zur Behandlung der Anämien mit Magenpräparaten, Klin. Wchnsch., Berl., 1930, ix, 2103.

[26]Henning, N., and Stieger, G.: Die Behandlung der perniziösen Anämie mit Magenschleimhautpräparaten, Klin. Wchnschr., 1930, ix, 2145.

[27]Bauer, R., and Wozasek, O.: Influence of ergotamine and of liver diet on functioning of liver, Wien. klin. Wchnschr., 1930, xliii, 1337.

[28]Faber, K.: Die Behandlung der perniziösen Anämie mit getrockneter Magensubstanz, Ugeskrift f. Laeger, Copenhagen, 1930, xcii, 467-468.

[29]Winge, K.: Pernicious anemia; treatment with desiccated stomach, Ugeskrift f. Laeger, Copenhagen, 1930, xcii, 511.

[30]Torrning, K.: Pernicious anemia treated with dried stomach; case, Ugesk. f. Laeger, Copenhagen, 1930, xcii, 510.

[31]Holboll, S. A.: Treatment of pernicious anemia with dried stomach, Hospitalstidende, Copenhagen, 1930, lxxii, 825.

[32]Ungley, C. C.: The stomach and pernicious anemia, Newcastle Medical Journal, 1929, x, 14-39.

[33]Lenhartz, H.: Ersetzt Organsubstanz aus Schweinemagen die Leber bei Be-

handlung der Biermerchen Krankheit? Deutsch. med. Wchnschr. 1930, lvi, 1872-1873.

[34]Dominquez, C., and Bizzozero, R. C.: Sindrome neuro-anemico; Tratamiento por la ingestion de e stomago de cerdo desecado, El. Dia Medico, 1930, iii, 49.

[35]Gutzeit, K.: Über die Behandlung des Morbus Biermer mit Magenpulver (Ventraemon), Münch. med. Wchnschr., 1930, lxxvii, 1625-1626.

[36]Allerton, G. T.: Desiccated hog stomach in pernicious anemia, Lancet, 1930, ii, 795.

[37]Godel, R.: Behandlung der perniziösen Anämie mit Ventraemon (Magenpräparat), Wien. klin. Wchnschr., 1930, xliii, 812-814.

[38]Herz, A.: Therapie der Anämien, Wien. klin. Wchnschr., 1930, xliij, 1189-1194.

[39]Burgess, J. P., and Morgan, J. E.: Effect of various stomach preparations in pernicious anemia, Proc. Soc. Exp. Biol. and Med., 1931, xxviii, 371-372.

[40]Lambin, P., and Steenhoudt, J.: Essai de traitement de l'anemie pernicieuse par des preparations d'estomac desseche, Bull. et Mem. de la Soc. Méd. des Hôp. de Par., 1930, xlvi, 986-991.

[41]Jagic, N., und Klima, R.: Zur Therapie der perniziösen Anämie mit Ventraemon, Wien. klin. Wchnschr., 1930, xliii, 877-878.

[42]Mouzon, J.: Stomach therapy in pernicious anemia, Presse méd., 1930, xxxviii, 847-850.

[43]Unpublished observations of the authors.

[44]Personal communication from Dr. R. M. McKean and Dr. E. A. Sharp. Paper in press.

The Adequate Treatment of Anemia*†

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Introduction

THE adequate treatment of anemia necessitates removal of the causes, whether proximate or remote, with attention to all aspects of a given case. The dependence to a greater or less degree of many cases of anemia upon an inadequate nutrition of the individual either produced directly by defects of the diet, or indirectly conditioned by a defect of the individual, makes the study of this aspect of the problem of primary importance. For this reason, it is our object not to discuss the use of special procedures such as transfusion of blood or splenectomy, but to emphasize the importance of a suitable diet and the use of optimal quantities of certain potent substances contained in food and shown to work almost as specifics for certain types of anemia. Adequate treatment, however, implies that the individual peculiarities of each patient and of his condition must be considered.

Pernicious Anemia

The adequate treatment of pernicious anemia is accomplished not by liver, kidney, stomach, brain, or potent preparations obtained from these organs, but by *enough* potent material, irrespective of the source, for the given individual throughout life. Successful treatment demands that the physician should know that the patient actually takes the amount prescribed. Sometimes the patient believes that he has been taking the proper amount, but after the physician inquires carefully, he discovers that the individual frequently omits a dose or has undoubtedly taken an insufficient amount. Confusion can arise from the fact that the amount of liver purchased will not be the amount of liver ingested. The amount prescribed should be the quantity to be swallowed. In preparing raw liver pulp or cooking liver, frequently from 20 to 35 per cent of the tissue is lost. Doctors and patients often believe that if

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†Read at the Baltimore Meeting of the American College of Physicians, March 27, 1931.

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the patient takes extract derived from 100 grams of an organ, he will obtain as much potent material as if he ingested 100 grams of the organ itself. Such is certainly not the case. Often the amount of extract derived from 100 grams of liver will be about as potent as 65 grams of prepared liver. The physician should know the potency of the preparation advised. He may obtain for himself such information by observations on the course taken by the reticulocytes or by referring to critical studies published by other persons. It is usually a relatively simple matter to initiate a remission in pernicious anemia by the daily feeding of various substances such as 200 to 300 grams of prepared liver or kidney, active extracts derived from 300 to 600 grams of liver, 150 or 240 grams of fresh whole pig stomach, or stomach mucosa or dried and defatted stomach prepared from this amount. Brain (Ungley) is about one-third as potent as liver. Failures will be found to be due to inadequate dosage, incorrect diagnosis or complications. Occasionally, unusually large doses are necessary, particularly because of complications and also sometimes owing to difficulty with absorption. When no response or a poor response has occurred with a known potent preparation, the amount should at least be doubled. In the case of a very sick patient, the entire dose of potent material for a week may be given within a few hours or even administered at one time to an unconscious patient by stomach tube. In this way the appearance of the response will be hastened.

Sometimes it is necessary to consider administering a potent preparation parenterally. Occasionally this method may be live-saving or be more convenient, and, under certain circumstances, it may have distinct advantages.†

The dose of potent material necessary for the maintenance of a normal red blood cell count and hemoglobin level and for the relief or prevention of progress of symptoms varies widely; in terms of liver extract* daily from that amount derived from 200 grams to that derived from 1200 grams of liver. The red blood cell count and hemoglobin alone should not determine the dose. These factors, considered together with the color index, the detailed character of the red cells (their size, volume index, etc.,) and white blood cells and blood platelets, and particularly the patient's signs and symptoms, should determine whether more, or rarely less, potent material should be taken. The object should be to make all aspects of the patient's blood normal and the patient himself as well as possible. The size of the cells can be fully as important a guide to dosage as the red blood cell count, but the patient's symptoms, especially if referable to the central nervous system, are as important as any laboratory examination in considering the amount of liver or potent substitute the individual should take. If a simi-

†See Castle, W. B. and Taylor, F. H. L., Intravenous Use of Extract of Liver. Jr. Amer. Med. Assoc., 1931; xcvi, (April 11), 1198; and papers by these authors on Intramuscular Use of Liver Extract, in press for Jr. Amer. Med. Assoc.

*Liver extract No. 343 Lilly (N.N.R.)

lar group of patients are compared, who have been relieved of severe anemia and who have had no definite subsequent relapse, (a condition always attributable to an *insufficient* amount of active principle or to complications,) it will be found that the patients who maintain the best health are usually the ones who take daily distinctly large amounts of potent material. It is important to adhere to the principle of supplying optimal quantities of effective substances to maintain the best possible health rather than to supply only enough to maintain definite improvement. The prescription of a proper amount of potent substance demands a knowledge of conditions that may inhibit its action. Infections, disorders of the liver, kidney, and other organs can hinder the effects of liver and potent substitutes. The usual adequate dose may need to be increased because of age or arteriosclerosis. In fact, for old people with arteriosclerosis, it usually will require at least double the amount of active principle to maintain health that is needed for individuals without complications below the age of 45 years. An increased amount of potent material is indicated when neurological symptoms cease to lessen and of course when neurological complications tend to show further progress. Many patients under liver treatment have had lesions referable to the neuro-muscular system develop or increase because they did not take enough potent material for their individual needs.

The treatment of the lesions of the nervous system seems best carried out by feeding with regularity large amounts of potent material—not merely the amount that will maintain a normal blood level. Whether the effect on the blood and the nervous system is due to one or more substances is open to speculation. Organs contain many substances not in extracts used for therapy and the latter in turn contain various materials, such as vitamin B_2 (G) in concentration, besides the substance crystallized by West and his associates, which is potent for blood regeneration in pernicious anemia. Possibly neuro-muscular symptoms may be affected more favorably by the feeding of organs than by extracts of equivalent potency for blood regeneration. Neuro-muscular symptoms often do not significantly change until the red blood cells have reached normal numbers and then may lessen very slowly. Since there is almost always some decrease in neurological symptoms with persistent large doses, the necessity of persevering with maximal amounts of active material is clear. If arteriosclerosis or complications are not present and especially if the nervous system lesions are of relatively recent origin or referable to the peripheral nerves, large amounts of liver or potent substitute will usually cause relatively rapidly pronounced improvement in the nervous manifestations. One can not expect, with long-standing advanced lesions of the central nervous system, great improvement in older people, but even in such cases, very large amounts of potent material over a prolonged period of time can be distinctly beneficial.

In carrying out adequate treatment, all aspects of the patient and his case

must be prescribed for. Care should be taken of the gastrointestinal tract and every effort made to obtain complete absorption of potent products. Appropriate, skillfully applied mechano-therapeutic procedures, mental hygiene, and many other sorts of matters must be wisely attended to. Certain restrictions often must be prescribed. One that has not been mentioned in the literature but which has been noted by Dr. West of New York, as well as by Dr. Murphy and ourselves, is that perhaps it is unwise for these patients to expose themselves to the sun sufficiently to tan their bodies intensively. Under such conditions it is possible that neurological manifestations have been distinctly aggravated and caused to progress with great rapidity.

Lack of attention to the diet may be a cause for a patient with pernicious anemia not to improve as much as possible. At times undesirable low color indices may occur when the red blood cell count is normal. Occasionally this state of affairs can be attributed to diets which for a long period of time have been scant in protein, vegetables and fruit. Under such conditions when the patient is taking ample extract of liver, the addition of iron may cause the hemoglobin to rise. The prescription of a proper diet is also obviously desirable. Sometimes, when the red blood cell count is about 4,000,000 per cu.mm. and hemoglobin about 70 per cent, both the red blood cell count and the hemoglobin can not be increased by large doses of potent substances effective in pernicious anemia. In some such cases, especially if pronounced arteriosclerosis or obvious complications are not present, iron in sufficient dosage will cause a distinct improvement not only in the blood but in the patient's sense of well-being.

If chronic blood loss is sufficient to cause anemia in a patient with pernicious anemia who has maintained a normal blood level with an adequate amount of potent material, he may develop hypochromic anemia which can be readily lessened by iron therapy.*

Other substances than iron, as well as food, may operate to improve the blood of pernicious anemia patients when they are in a state of remission. For example in rare instances hypothyroidism and pernicious anemia may be present in the same individual. The relief of anemia may not be completely possible without the administration of a potent thyroid preparation in addition to adequate therapy for pernicious anemia.

Frequently, after the patient appears to have improved as much as possible as a result of taking for months, not weeks, distinctly large quantities of potent material, the physician is confronted with this question which the patient more often asks before a month has passed by, "How much less medicine can I now take?" The answer is always difficult. It is safe, when the amount has been distinctly large, to curtail the dose somewhat. One should be prepared to return to large doses again on relatively slight provocations. It is unwise, however, for any patient with pernicious anemia to

*A chart illustrating this state of affairs for one of our cases in given in an article by R. T. Beebe and G. E. Lewis in the Am. Jr. Med. Sci., 1931; clxxxi (June), 796.

take daily less than 200 grams of prepared liver or the amount of potent material equivalent to that contained in the most potent commercial extracts derived from 300 grams of liver.

An occasional patient with pernicious anemia may remain, as before the days of liver therapy, in a state of splendid remission without any particular treatment for a year and even more, but this in no way contraindicates the important principle for the patient with pernicious anemia to understand—namely, the necessity of continuing to take indefinitely and with regularity the quantity of potent material optimal for the given case.

Rarely cases with a blood picture of pernicious anemia occur with normal amounts of free hydrochloric acid in the gastric contents. Some such cases have arisen as the result of partial removal of the stomach or disorders of the lower intestinal tract, and some are cases of sprue. The principles of treatment are no different under these circumstances, just as it is unnecessary to administer hydrochloric acid to the case of pernicious anemia with gastric achlorhydria. This is because Castle has shown that individuals may have a normal gastric acidity yet lack the factor which is absent from the stomach in all pernicious anemia patients, who almost always have achlorhydria. This factor, which occurs in the normal stomach, when brought in contact with beefsteak, liberates a substance that is effective in pernicious anemia. It is likewise pointed out here that achlorhydria often occurs in patients with idiopathic hypochromic anemia, but their gastric secretions contain the gastric factor lacking in pernicious anemia. One should recognize that it is not achlorhydria that conditions the state of pernicious anemia, but the lack of a particular factor secreted by the normal stomach which is not hydrochloric acid, pepsin, rennin, or lipase.

Anemias that Respond to Iron

The principles of the adequate treatment of anemias that can respond to iron are essentially the same as those set forth for pernicious anemia. Iron may have pronounced favorable effects on blood regeneration. The many conflicting statements in the literature concerning the value of iron therapy are probably dependent upon deductions from circumstances that were not the same. Iron may control important activities within cells; it influences growth and thus affects the body metabolism besides supplying this element for hemoglobin formation. The course taken by the reticulocytes will foretell, if properly evaluated, the effectiveness of iron therapy in a given case. The character of the curve for the reticulocytes in response to iron is somewhat different from that which appears with liver therapy in pernicious anemia. Likewise data concerning the reticulocyte increase from iron administration must be interpreted slightly differently than those for pernicious anemia.

There are various sorts of so-called "secondary" anemias that can be promptly alleviated by the use of iron in suitable doses. Anemia due to

chronic blood loss usually lessens rapidily under iron therapy. Patients with "secondary" anemia dependent upon either no well-recognized cause or associated with certain dietary deficiencies or altered gastrointestinal function, or both, are among those benefited often by iron. Such cases are common in women and the anemia may be enhanced by blood loss, pregnancy, infection, and other complications. The condition known as chronic chlorosis or hypochromic achlorhydric anemia is distinctly one in which the patient is favorably affected by large doses of iron. The rôle played by the disturbed gastric function is unknown but, indeed, may be most important.

Infections and various complications or conditions inhibit the action of iron comparable to the effect of such disorders on the treatment of pernicious anemia, so that brilliant results from iron therapy can not be expected in anemia of infectious origin. Likewise iron cannot influence aplastic or myelophthisic bone marrows or be definitely effective when a distinct degree of abnormal blood destruction continues to be operative as in chronic hemolytic jaundice.

The principle of giving enough iron to accomplish the best possible result must be adhered to. Often small doses of iron (75 mgs.) in the form of an iron salt such as ferrous carbonate, iron citrate, or iron and ammonium citrate or reduced iron may cause a rise of reticulocytes and slow improvement of the patient, when larger doses (0.5 gram) will produce brilliant and rapid results. Sometimes, especially in chronic chlorosis, a daily dose of 75 mgs. of iron *per se* contained in a salt will produce no effect whatsover, when 350 mgs. of iron will cause pronounced benefit. Although iron is apparently more effective when absorbed from an acid than from an alkaline medium in the upper gastrointestinal tract, if sufficient iron is given the ultimate benefit observed will be the same. Many papers have appeared concerning whether one sort of iron preparation is more effective than another. Although much more knowledge concerning this subject and the physiology of iron metabolism is desirable, it would seem that the form in which iron is prescribed is less important than that it is in sufficiently large quantities and in such a state that it can be readily absorbed. For this reason it would seem wise to give a salt of iron preferably already dissolved. Metallic iron may need solution by the body and pills or capsules containing iron compounds may pass through the gastrointestinal tract intact. Iron and ammonium citrate is a readily soluble inexpensive salt which may be given dissolved in milk. Because of the occasional diarrhea, induced by the large doses necessary, it is well to begin with a dose of about half a gram three times a day and increase to the generally useful dosage of two grams three times a day.

It is probably unwise to stop iron therapy as soon as the blood has returned to normal in a case that can be considered truly curable as, for instance, a case of chronic blood loss with the blood loss stopped. Presumably at the time the number of red blood cells and hemoglobin have

reached normal, the body is still deficient in iron, so that it is desirable for the patient to continue taking iron for at least some weeks after the blood appears to be completely regenerated. Moreover, there are undoubtedly cases of chronic chlorosis and somewhat similar cases with relatively higher color indices, in which the cause of the anemia is not clear-cut, that will inevitably relapse unless iron therapy is continued indefinitely. It is such cases that may have a defect in the utilization of iron, dependent in some way on abnormal gastrointestinal function comparable perhaps to the defect in gastric secretion that occurs in pernicious anemia. Adequate treatment of this type of patient demands frequent observations and the insistence of iron therapy presumably throughout the life of the patient. Omission of iron may cause relapse in from a few weeks to months or sometimes not for several years. Some data at hand suggest that after iron is omitted a relapse will occur sooner in the patients who have taken iron for a short rather than a long period of time.

Although iron alone can be very effective, there are other factors that can accelerate blood formation in anemias influenced by iron. Copper, under certain circumstances, probably especially in infants, as Josephs has shown, may enhance the blood-regenerating power of iron. Hart and his associates first demonstrated this effect in young rats with anemia produced by the feeding of a whole milk diet. The iron salts commonly prescribed for patients usually have copper in small amounts mixed with them and perhaps some of the effects credited to large doses of iron should be attributed to the synergetic action of copper and iron.

Liver contains many substances other than the active principle effective in pernicious anemia. The commercial extracts prepared particularly to supply the latter substance are effective in certain other megaloblastic anemias resembling typical Addisonian pernicious anemia. They are occasionally effective in severe anemias not suspected to be associated with a megaloblastic bone marrow. Usually these extracts are not significantly effective in "secondary" anemia and undoubtedly many patients have wasted money and effort in buying and taking such products that can not be expected to benefit them. Whole liver, in the large amounts effective for pernicious anemia, may have a remedial effect in many cases that can be benefited with iron. This effect is certainly not attributable only to the iron contained in liver. Whipple and his associates have shown that liver contains, in addition to iron, material effective in the promotion of hemoglobin regeneration in anemia due to chronic blood loss in dogs. They have isolated a fraction of liver potent in this respect that is distinct from the fraction effective for pernicious anemia. In their animals, supplementing this liver fraction with small amounts of whole liver may increase the total output of hemoglobin above the level due to the liver fraction alone. Whipple has also shown in his dogs, and we have observed in the clinic, that liver extract for pernicious anemia is essentially inert in anemia due to chronic blood loss, but upon supplementing it with a relative-

ly little whole liver, the effect in the dogs and in an occasional human case is greater than the influence of either alone. Clinical observations show that large amounts of liver can be effective in the regeneration of blood following chronic blood loss and in some other cases of "secondary" anemia, but that it is usually less potent and far less easy to take than iron salts. Sometimes liver will have little or no effect on anemias of ill-defined origin in which iron will produce rapid blood regeneration. The addition of liver, however, to the diet of a patient improving with iron can act sometimes to accelerate blood regeneration, especially as the hemoglobin approaches the normal level.

Iron apparently acts to produce blood regeneration by an effect additional to supplying the element for hemoglobin formation. It alone can not supply the loss from the body of material valuable for hemoglobin formation, but liver and kidney particularly, as well as other foods, contain material necessary for new hemoglobin fabrication. Although iron alone can often produce, with a satisfactory diet, excellent results, it is to be recognized that liver or potent substitutes with iron may cause maximal blood regeneration. If treatment with iron and liver, or a suitable substitute, is prescribed because the combination offers the greatest chance for the greatest improvement in anemic patients, some patients will take material that is unnecessary, and knowledge regarding the effectiveness and action of substances will not be obtained. Sometimes one can demonstrate clearly the influence of different materials by feeding for periods of time first one and then another substance.

We have seen cases that were certainly not ones of pernicious anemia, with the red blood cells about 2,000,000 per cu.mm. and the color index close to one, that responded to liver extract effective in pernicious anemia with rapid regeneration of the red blood cells to normal, but with only slight increase of the hemoglobin over a period of weeks. At that stage, however, iron caused rapid regeneration of hemoglobin. Cases also have been observed that were inert to alcohol precipitated liver extract, but in which whole liver slowly produced regeneration of the red cells to normal with some rise of hemoglobin. In these cases, upon the addition of iron, there followed a rapid rise of hemoglobin to normal. When iron alone is given the hemoglobin and the red blood cells often increase rapidly to normal. Sometimes the red blood cells rise quickly, for example from 3,000,000 to 4,500,000 per cu.mm. and the hemoglobin from 40 to 70 per cent. Without further treatment than iron and a satisfactory diet there may then be a very sluggish rise of the hemoglobin and red cells, but sometimes in such cases if whole liver is added, the hemoglobin rapidly rises to normal and the red blood cells promptly increase still further. It is thus desirable to learn the effect of different factors on blood regeneration in not only various sorts of anemias, but in anemias due to the same cause under varying conditions. Important conditions that may vary are the degree of anemia, the character of the red blood cells, the amount of reserve

supplies of blood-building materials in the body, the secretions of the stomach, and other states of the gastrointestinal tract.

The Importance of Diet

The diet of each patient with anemia must be carefully considered and individually prescribed, or adequate treatment will not be given. The relationship between diet and anemia was mentioned in the 17th century. Although the scientific foundations for the value of food for patients with anemia were laid by Menghini in 1746 and by Verdeil in 1849 when they showed by feeding animals food rich in iron that this element could be increased in their blood, it is only within recent years that the importance of diet in causing or alleviating anemia has been broadly recognized. Even so, knowledge concerning the influence on blood formation of different sorts of food or substances they contain is in its infancy and there is need for a wider appreciation of the fact that anemia often can be wholly or partially related to the partaking of an unsuitable diet for a period of years.

A carefully obtained and detailed history concerning the patient's dietary habits throughout life often will suggest a reason for anemia and can lead to the selection of a desirable diet for a given case. The part played by chronic digestive disorders, such as colitis with diarrhea and achlorhydria with or without other altered physiological mechanisms in preventing the absorption or utilization of factors necessary for blood formation is always for evaluation. Temporary gross dietary deficiencies do not produce significant symptoms but departure from an optimal diet, even if slight, can produce ill health when operative over a long period of time and especially if combined with digestive disturbances. For example, it is common to observe women who eat little or no breakfast, a lunch composed chiefly of concentrated carbohydrate foods and a fairly satisfactory evening meal who have slight anemia and often constipation. In such cases, without other cause for the anemia than improper food, an ordinary well-balanced diet rich in fruits and green vegetables and containing ample animal protein not only can correct the anemia, but improve much more the patient's general sense of well being. Iron or liver or both may accelerate the improvement.

In known chronic vitamin deficiencies in man anemia is a symptom. The anemia may be dependent upon other factors than the lack of a given vitamin, but at times as in chronic scurvy in adults it can be related directly to the lack of vitamin C. In such instances iron and liver extract potent for pernicious anemia are not effective, but food rich in vitamin C can produce a reticulocyte response and rapidly lessen the anemia. Anemia can also arise from long-standing deficiency of protein and lessen when ample protein food is supplied.

These examples of ill-defined and distinct dietary defects simply hint at the many varieties of defective diets that can play a rôle in the production of anemia. In such conditions as well as in others, food alone, excluding liver or potent substitutes, can restore the blood to normal, although often in

such cases, iron with or without liver is necessary for effective or rapid results. In anemia, however, the body is probably often depleted in the products needed to build cells and hemoglobin; such occurs, for example, in chronic blood loss and in long-standing dysentery as well as when the food intake has been obviously chronically deficient in one or more respects. Iron and liver extracts indeed may produce great benefit, but in order to establish a completely normal state of affairs, other elements are required for the manufacture of blood which can be supplied by food for optimal nutrition. For example, we have demonstrated that patients with anemia from prolonged chronic blood loss treated with iron regenerate their blood more slowly when their diet is composed of crackers and milk than when it contains muscle meat, vegetables, and fruits.

It is only desired to indicate here that the greatest improvement in the anemic patient will be obtained when, in addition to distinctive therapy, attention is paid to the diet. The patient's weight, age, and state of his digestive system must be considered in prescribing the diet. Simply because diarrhea exists, the diet must not be abnormal in quality. In certain vitamin deficiencies, looseness of the bowels may be a result and the prolonged diarrhea may increase the cause. In such cases, the physical state of the food may need modification; but the diet should contain optimal quantities of food for the best possible nutrition. Certain foods may delay the digestion of other foods or upset the digestive functions; for example, fat, except in small amounts in the diet of many pernicious anemia patients, often disturbs the digestive process as well as leads to an undesirable gain of body weight. One must not only consider for a given anemic individual the selection of food from the point of view of furnishing ample blood-building materials and supplying food for optimal nutrition, but also take into account the preparation of the food and the exact dishes to be served.

The Importance of Attention to Every Phase of Each Case

Large amounts of whole liver, together with big doses of iron and an adequate well-balanced diet offer the greatest chance of improvement to the anemic individual. Such treatment, however, is of a "shot gun" nature and will not determine the exact importance and action of different factors. Treatment given routinely in this manner will tend to lead to neglect of all the aspects of the patient's case. Every phase of each case must be properly considered and treated and the patient, a human being himself, must never be neglected.

An example of where attention to the patient's conduct of life and his diet had a profound effect on his sense of well-being is as follows:

A man of 60 years of age with pernicious anemia in a state of remission for two years had taken regularly sufficient liver extract to maintain his red blood cells at about 4.7 million per cu.mm. and hemoglobin at 80 per cent. He had suffered for the last eight months of this time from weakness, fatigue, various symptoms referable to an unstable vaso-motor system, considerable intestinal flatulence and

mental depression. Numbness in his hands developed, but varied greatly from hour to hour in its intensity. He had eaten an excess of sugar and concentrated starch food and it was believed that he had an intestinal carbohydrate indigestion. He, also, was confronted with anxiety regarding his children and had lost much sleep. Furthermore, he had discussed the symptoms of pernicious anemia with other individuals who suffered from this disease and believed he had a rapidly progressive disorder of his spinal cord. Prolonged optimistic talks with the patient, curtailment of the carbohydrate in his diet, regular moderate exercise and longer hours in bed at night, without change in the daily dose of liver extract caused within a few weeks pronounced improvement in his health. The numbness in his hands disappeared, the gastrointestinal tract functioned properly and his strength returned and coincidently the hemoglobin increased over ten per cent and the red blood cells about 400,000 per cu. mm.

In the future, more will be learned about the relation of the gastrointestinal tract to anemia and to other chronic disorders. Also knowledge will be broadened concerning the rôle that diet and substances contained in food play in the etiology and treatment of anemia. This will be accomplished from observations at the bedside expanded in the laboratory by not only trained clinical investigators, but by all practitioners of medicine. This is one of the most important ways that knowledge is obtained that leads to the alleviation of suffering and the prevention of disease.

Complement Fixation in the Diagnosis of Amebiasis*†

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By the term "amebiasis" is meant the condition brought about in the human body by the invasion of the tissues of the intestines by *Endamoeba histolytica*, the ameba causing that type of dysentery called "amebic dysentery". Most unfortunately, from the standpoint of a clear understanding of the importance of this parasite as a cause of disease in man, the term "amebic dysentery" has, until quite recently, been synonymous with "amebiasis" in the minds of the vast majority of the medical profession. In addition, the conception that infection with *Endamoeba histolytica* occurs only in the tropics and sub-tropics has led the profession far astray regarding the real importance of this parasite to human medicine throughout the world.

As the result of many surveys by competent investigators, of all classes of people in many temperate regions, as well as in the tropics and subtropics, we know that *Endamoeba histolytica* is world wide in distribution and that, so far as the United States is concerned, from five to ten per cent of individuals harbor this parasite. The percentage is far higher in some parts of our country, while it is somewhat lower in others, but a conservative estimate places the infection of the general population of the United States at about five to ten per cent. Fortunately, most of the individuals infected do not show marked symptoms of their infection, but clinical observations of infected individuals have shown that from 20 to 50 percent do have symptoms, and that in most such individuals proper treatment resulting in the elimination of the parasite, also results in the disappearance of the symptoms.

As long ago as 1891, Dock[1] demonstrated that amebiasis is not a tropical disease, and that amebic lesions of the intestine could be present in persons free from dysentery and with no history of the infection. The observations of Dock were confirmed in 1910 by Musgrave[2], who demonstrated at autopsy that marked ulceration of the intestine may occur even though no recognizable symptoms are noted, and it is well known that abscess of the liver may occur in individuals with no

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†Read at the Baltimore Meeting of the American College of Physicians, March 25, 1931.

history of diarrhea or dysentery. In 1921, I[3] called attention to the atypical symptoms often present in individuals infected with *Endamoeba histolytica*, symptoms having little in common with the classical symptom-complex known as "amebic dysentery", and to the great importance of regarding the latter condition as the most severe result brought about by the invasion of the intestine by this parasite.

Within recent times, an immense amount of evidence has accumulated demonstrating that marked deviations from health may be produced by this parasite without dysentery ever occurring and it may be truly stated that for one case of amebic dysentery there are hundreds of cases of amebic diarrhea or other conditions due to the parasite. In those individuals showing no symptoms of the infection we must believe that an equilibrium has been established between the host and the parasite, and that the damage done by the parasite is repaired immediately. However, this resistance to the parasite may be broken down in various ways, so that the recognition of the infection and the elimination of the parasite is important, even in these more fortunate individuals.

Whether *Endamoeba histolytica* can live in the lumen of the human intestine without invading the tissues is a question now being carefully investigated, but personally, it is believed that in every individual harboring this parasite some injury to the tissues is produced, and that the amount of this injury directly influences the character of the symptoms present, or their absence. If comparatively few amebae are invading the tissues of the intestine, symptoms may be entirely absent, the minute lesions produced by the amebae healing promptly, while, if larger numbers invade the intestinal walls, the symptoms may vary from those characteristic of mild invasion to those recognized as typical of the symptom-complex known as "amebic dysentery." The important fact to be borne in mind, from the recent studies of this infection, is that *Endamoeba histolytica* is world wide in distribution and is the cause of much invalidism hitherto unrecognized as being due to this parasite. As Lynch[4] says: "We have come, then, from knowing amebic dysentery as the disease produced by *Endamoeba histolytica,* to the point where this is recognized as the uncommon acute, or relatively acute, phase of the disease, while there exists in the population at large an incidence of latent infection conservatively estimated at from five to ten per cent, in many, if not all, of which it is the belief of careful and competent experienced men that there is a chronic low-grade disease of devitalizing quality but diagnosable only on finding the amebae."

The recognition of these latent infections with *Endamoeba histolytica* is most important and, at the present time, rests upon the demonstration of the parasite in the feces of the infected individual. When the services of a competent protozoologist, or of one trained in the study of the various species of amebae occurring in the intestine of man (of which there are no less than five species) is available,

TABLE I

Illustrating the time of Disappearance of the Complement Fixation Reaction for *Endamoeba histolytica* after Treatment

Case No.	Date of Examination	Complement Fixation Test for *E. histolytica*	Feces Examination for *E. histolytica*	Date Examined After Treatment	Complement Fixation Test for *E. histolytica*	Feces Examination for *E. histolytica*	Days after Cessation of Treatment
1.	July 17	+ + + +	Positive	Aug. 27	—	Negative	21
2.	Aug. 2	+ + + +	Positive	Sept. 25	—	Negative	30
3.	Dec. 29	+ + + +	Positive	Jan. 31	—	Negative	18
4.	Jan. 12	+ + + +	Positive	Jan. 31	+ +	Negative	5
5.	July 6	+ + + +	Positive	Sept. 17	—	Negative	21
6.	July 23	+ + + +	Positive	Sept. 9	—	Negative	28
7.	Dec. 27	+ + + +	Positive	Jan. 23 Feb. 6 May 22	+ + + + — + + + +	Negative Negative Positive (relapse)	14 20 130
8.	July 23	+ + + +	Positive	Oct. 25	—	Negative	60
9.	Jan. 16	+ + + +	Positive	Feb. 12	—	Negative	14
10.	Mar. 20	+ + + +	Positive	May 15 June 10	— —	Negative Negative	21 46
11.	Feb. 27	+ + + +	Positive	June 10 Nov. 11	— —	Negative Negative	56 206
12.	June 19	+ + + +	Positive	July 7	—	Negative	3
13.	July 31	+ + +	Positive	Aug. 29	—	Negative	7
14.	Sept. 11	+ + +	Positive	Oct. 16	—	Negative	12
15.	Sept. 16	+ + + +	Positive	Oct. 18	—	Negative	11
16.	Oct. 2	+ + + +	Positive	Nov. 6	—	Negative	14
17.	Nov. 20	+ + + +	Positive	Jan. 15	—	Negative	14
18.	Sept. 6	+ + + +	Positive	Sept. 28	—	Negative	6

NOTE: In two of the cases cited the Wassermann and Kahn tests gave four plus reactions and these remained so after the disappearance of the positive reaction for infection with *Endamoeba histolytica*.

the diagnosis can be made, but there is great difficulty in differentiating the various amebae of the human intestine and such a differentiation can be made only by one with training and experience. *Endamoeba histolytica* is the only pathogenic ameba occurring in the intestine and hence has to be differentiated from the four other species of ameba that occur there, for a diagnosis of amebiasis based merely upon finding an ameba in the feces is absolutely worthless. The development of some method of diagnosis which would eliminate, if possible, the necessity of differentiating the amebae, would obviously simplify the problem, and it has been with the hope of doing this that I have endeavored to apply the principle of complement fixation to the diagnosis of amebiasis. It has been found possible to do this and in previous publications[5,6,7] I have described such a test and the results obtained with it.

As regards the technique it may be stated briefly that it follows the standard method for the complement fixation test for syphilis used in the U. S. Army laboratories. The human hemolytic system is used and the blood sera are inactivated by heating at 56°C. for one-half hour. The antigen used is an alcoholic extract of cultures of *Endamoeba histolytica* grown upon the Boeck-Drbohlav medium.

Material

The greater number of the individuals tested have been patients in Walter Reed U. S. Army General Hospital where the test is now used as a routine procedure in suspicious cases. The material has included patients suffering from a great variety of disease conditions and in addition numerous normal persons have been used as controls. The result of each test is checked by microscopic and cultural examinations of the feces of the individuals tested for the presence or absence of *Endamoeba histolytica*, and the results reported in this communication have all been checked by such examinations.

Results of the Test

Considerably more than 1000 individuals have been tested to date, but this report will concern only those tests in which the feces have been checked for the parasite, numbering 786, of which 110, or 13.9 per cent, gave a positive reaction, while 676, or 86 per cent, gave a negative reaction.

In the vast majority of cases the reaction with this test is very clear cut, being either three plus or four plus when read on a four plus scale. Of the 110 positive cases, no less than 91 gave a four plus reaction and 17 a three plus reaction. It should be remembered in considering the number of positive cases that many of the patients at the Walter Reed General Hospital are soldiers or officers who have served in tropical regions, and that in the vast majority of cases tested there were symptoms indicating some disease condition located in the gastro-intestinal tract.

In the 110 positive cases, a check of the feces for *Endamoeba histolytica* resulted in the demonstration of this parasite in 94 cases, of 85.4 per cent. In 16, or a little over 14 per cent, we were unable to find the parasite, although this negative finding cannot

be considered as conclusive owing to the fact that in most of these cases it was not possible to make more than one or two examinations of the feces. It has been definitely shown that a single examination of the feces is often negative in positive cases and that a single examination demonstrates only about one-third of the total infections with this parasite.

Of the 94 positive cases showing the presence of *Endamoeba histolytica* in the feces, 66 showed infection with *Endamoeba histolytica* alone; 12 were mixed infections with *Endamoeba histolytica* and *Endamoeba coli*; 6 with *Endamoeba histolytica* and *Endamoeba nana;* 2 with *Endamoeba histolytica, Endamoeba nana* and *Endamoeba coli;* 2 with *Endamoeba histolytica* and *Chilomastix mesnili*; 4 with *Endamoeba histolytica* and *Giardia intestinalis* and 2 with *Endamoeba histolytica* and *Trichomonas hominis.*

There were 676 individuals tested giving a negative result, and of these, *Endamoeba histolytica* was found in 8 cases or 1.1 per cent. Three of these were acute cases of amebic dysentery; one was a case of abscess of the liver; three showed indefinite gastro-intestinal symptoms; while one was symptomless. From these findings it is evident that all persons infected with this parasite do not give a positive reaction but that the percentage of such individuals is apparently very small.

Of the 676 patients giving a negative reaction no less than 220, or 32.5 per cent, were infested with other species of protozoa. There were 100, or 14.7 per cent infested with *Endamoeba coli*; 64, or 9.9 per cent, infested with *Endamoeba nana*; 3, or 0.4 per cent, infested with *Iodamoeba williamsi*; 26, or 3.8 per cent, with *Chilomastix mesnili*; 16, or 2.3 per cent, with *Trichomonas hominis,* and 11, or 1.6 per cent, with *Giardia intestinalis.* There were 14 mixed infestations with *Endamoeba coli* and *Endamoeba nana;* 6 with *Endamoeba coli* and *Chilomastix mesnili*; 4 with *Endamoeba coli* and *Giardia intestinalis,* and 3 with *Endamoeba coli* and *Trichomonas hominis.*

The infestation of the intestine of man by species of amebae other than *Endamoeba histolytica* does not result in a positive complement fixation reaction. Thus, of the 676 patients giving a negative reaction no less than 164, or 23.5 per cent, were infested with some other species of ameba, but none of these cases gave even a partial reaction with the test.

As practically all of the 676 individuals giving the negative reaction were patients in a large general hospital and were suffering from a wide range of acute and chronic disease conditions, it is justifiable to conclude that this test is not positive in other diseases with the exception, as noted later, of certain rare cases of syphilitic infection.

Disappearance of the Complement Fixation Reaction after Treatment

It has been our invariable experience that after treatment resulting in the disappearance of *Endamoeba histolytica,* the positive complement fixation reaction becomes negative. The rapidity with which the reaction becomes negative depends on the

efficiency of the treatment. The earliest disappearance of the reaction after cessation of treatment resulting in the disappearance of *Endamoeba histolytica* from the stools has been five days and the longest period 60 days. In the longer periods it is probable that the reaction disappeared much more rapidly than indicated, as in some of these cases tests were not made until a long period had elapsed. In most of the cases the reaction disappears within three weeks after the disappearance of the organism from the feces following treatment. In several cases relapses have occurred and the reaction has again become positive, becoming negative again after proper treatment. The disappearance of the positive reaction after treatment demonstrates the specificity of the reaction. It has been noted that in cases giving a positive Wassermann and Kahn reaction that the complement fixation reaction for *Endamoeba histolytica* has become negative while the Wassermann and Kahn reactions remain positive. Table I illustrates the results obtained with the complement fixation test before and after treatment, the cases selected being those most typical of the varying results as regards time of disappearance of the reaction.

Relation of the Wassermann and Kahn Reactions

The antigen used in the complement fixation test for infection with *Endamoeba histolytica* is an alcoholic extract of cultures of the organism mixed with the bacteria which may be growing with it in the cultures and it also contains some material derived from the culture medium itself. Early in our work it was believed that the results obtained with the test might be due to a non-specific substance present in the extract, similar to those in extracts used as antigens for the Wassermann and Kahn tests. In order to obviate such a source of error, and ascertain whether the positive results were due to syphilis, all of the sera tested have been subjected to both the Wassermann and Kahn tests in addition to the complement fixation test for *Endamoeba histolytica*. This check has shown that 15, or 13.6 per cent, of the 110 individuals giving a positive reaction with the complement fixation test for *Endamoeba histolytica* also gave a positive Wassermann and Kahn reaction, while 95, or 86.3 per cent, gave a negative Wassermann and Kahn reaction. On the other hand, of the 676 individuals giving a negative reaction with the complement fixation test for *Endamoeba histolytica*, 56, or 8.2 per cent, gave a positive Wassermann and Kahn reaction, while 620, or 91.7 per cent, gave a negative Wassermann reaction and 618, or 91.4 per cent, gave a negative Kahn reaction. It will thus be seen that about five per cent more individuals gave a positive Wassermann and Kahn reaction in those giving a positive result with the complement fixation test for *Endamoeba histolytica* than in those giving a negative result. It was also significant that of the 15 individuals giving a positive reaction with all three tests, no less than nine failed to show *Endamoeba histolytica* in the feces, although it must be stated that in these cases not more than two

examinations were made of the feces. If we admit that all found negative were free from infection with *Endamoeba histolytica,* it would follow that the positive reactions were due to infection with syphilis, but in interpreting these figures it should be remembered that a considerable number of the sera tested were selected at random from specimens submitted to the Serological Laboratory of the Army Medical School, for the Wassermann and Kahn tests. However, the fact that a considerably larger percentage of cases giving a positive reaction with this test also gave positive Wassermann and Kahn reactions, taken with the failure to find *Endamoeba histolytica* in the feces in more than half of these cases, leads us to conclude that, in rare instances, patients suffering from syphilis may give a positive result with this test and that this disease should be eliminated, if possible, in patients giving a positive reaction, unless the result is supported by finding the parasite in the feces.

Practical Value of the Complement Fixation Test for Amebiasis

At the present time the practical value of the test we have been discussing is limited by the difficulty of preparing the antigenic extract, which has to be prepared from a large number of cultures of *Endamoeba histolytica,* and the difficulty of maintaining these cultures is not inconsiderable even to one accustomed to cultivating this organism. However, this difficulty is not insuperable, but the technique of the test is such as to render it impossible of application except in laboratories where the services of a protozoologist and a serologist are available. As shown by the results which have been obtained with the test, it is of considerable value in the diagnosis of cases of amebiasis, and the physicians at Walter Reed General Hospital, for whom the tests have been made, are unanimous in the statement that it has been of practical value to them in diagnosis. Efforts have been made to simplify the method of preparing the antigenic extract, or to render it more powerful, but to date these efforts have been in vain, so that it cannot be said that at the present time the test is on the practical basis that a complement fixation test should be, before it is relied upon *alone* in the diagnosis of a specific infection. However, it is felt that the technique will be simplified and that eventually the test will be of greater practical value.

Conclusions

The following conclusions have been justified by the results of the complement fixation test for amebiasis obtained to date:

1. There occur in the blood serum of individuals infected with *Endamoeba histolytica,* specific substances which can be demonstrated by complement fixation when alcoholic extracts of cultures of this parasite are employed as antigens.

2. These complement fixing bodies disappear from the blood serum after treatment resulting in the disappearance of *Endamoeba histolytica* from the feces of the infected individuals.

3. Individuals free from infection with *Endamoeba histolytica* very rarely give a positive reaction, and in the very small percentage of cases in which infection with this parasite could not be demonstrated it is probable that the failure to demonstrate it was due to an insufficient number of examinations of the feces.

4. Individuals infested with *Endamoeba coli, Endamoeba nana, Iodamoeba williamsi, Chilomastix mesnili, Trichomonas hominis* or *Giardia intestinalis* do not give a positive reaction with the complement fixation test.

5. With the exception of rare cases of syphilis, the complement fixation test for amebiasis does not occur in individuals suffering from other infestations or diseases.

6. Positive complement fixation reactions occur in individuals suffering from symptoms of infection with *Endamoeba histolytica*, and also in those in whom symptoms are absent, i.e., the so-called "healthy carrier" of the parasite. It has been noted that when symptoms are very acute the complement fixation reaction is sometimes absent or weak.

REFERENCES

[1]Dock, G.: Centralbl. f. Bakt., etc., 1891, x, 227.

[2]Musgrave, W. E.: Philippine Jr. Sci., 1910, v. 229.

[3]Craig, C. F.: Jr. Am. Med. Assoc., 1921, lxxxviii, 19.

[4]Lynch, K. M.: Protozoan parasitism of the alimentary tract, 1930, p. 77, New York.

[5]Craig, C. F.: Am. Jr. Trop. Med., 1927, vii, 225.

[6]Craig, C. F.: Am. Jr. Trop. Med., 1929, ix, 277.

[7]Craig, C. F.: Jr. Am. Med. Assoc., 1930, xcv, 10.

Pathological Classification of Goiter and Its Clinical Significance*†

By Wm. Carpenter MacCarty, M.D., F.A.C.P., *Rochester, Minnesota*

In 1912,[2] a report of more than two thousand goiters revealed that they divided themselves into two great groups: those which were thyroid shaped and those which were nodular. Both groups were then studied from the standpoint of their structural and functional units and these were correlated with the clinical pictures. Since then, 32,479 goiters have been examined grossly and microscopically. In this large amount of material universal facts and principles have been sought in the hope of giving to practicing physicians and surgeons some simple clinical classification based on gross and microscopic characteristics which have become known to be associated with definite symptoms.

It is interesting to note what Boothby,[1] a clinical physiologist, has said about the classification of goiter: ". . . . the anatomic changes (except infection and malignancy) are not primary and, therefore, are not the fundamental cause of the various diseases of the thyroid gland. In consequence it seems advisable to attempt the interpretation of thyroid disease and the accompanying pathologic changes in the light of the changes in physiologic activity rather than in the terms of pathologic anatomy. . . . To meet the needs of the clinician, however, a classification of thyroid disease cannot with the knowledge at present available, be expressed entirely in terms of physiologic activity any better than in terms of gross or microscopic pathology; nor can it be based entirely on etiology."

It is a recognition of this fact over many years that has led to the continued and constant study of gross anatomy, histology and cytology in the series reported. Clinical classifications always become more intelligible when the finer structures, structural relationships, functions, and functional relationships are clearly understood. In this study an attempt has been made to present the fundamentals of structure, and to correlate them with the well-known clinical manifestations of disease of the thyroid gland.

The structural units of the thyroid gland, under all conditions, are very definite and constant. These may be seen in the accompanying diagrammatic drawing (figure 1). Thus in the early stages of fetal development one finds in the neck a mass of cells without acinic or follicular arrangement

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(figure 1, *a*). These cells are the undifferentiated fetal thyroid gland. Later they assume acinic form (figure 1, *b*). During this change the whole mass of fetal cells assumes the gross form of the adult thyroid gland. During postnatal life this form is maintained unless altered by pathologic conditions. The normal adult thyroid gland is composed of acini which are approximately spheroidal in shape, lined by low cuboidal or spheroidal cells (figure 1, *c*). The lumen of the normal acinus is filled with a "colloid" material. There is fairly constant uniformity of size of the acini, although one occasionally finds acini which are fetal in size.

In my experience there are only four types or conditions of acini which are sometimes associated with abnormal or pathologic signs and symptoms. These are the fetal acinus (figure 1, *b*) one finds in adenomas, the dilated acinus (figure 1, *d*) found in the simple colloid goiter, the acinus lined by hypertrophic columnar cells (figure 1, *e*) seen in association with hyperthyroidism which occurs in both thyroid shaped goiters and nodular goiters, and the acinus lined by atrophic cells seen in myxedema and cretinism.

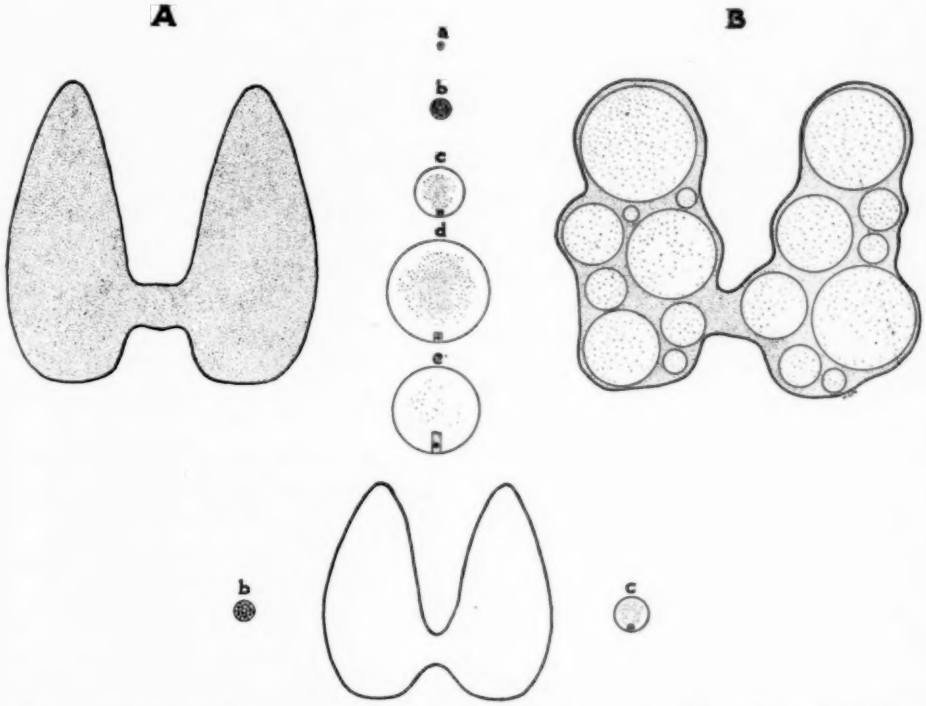

FIG. 1. Diagrammatic representation of all types of hypertrophic goiters (with the exception of pure inflammations and malignancies); *A*, hypertrophic symmetric goiters; *B*, hypertrophic nodular goiters; *a*, undifferentiated fetal thyroid cells; *b*, typical fetal acinus; *c*, normal adult acinus; *d*, distended acinus filled with colloid and lined by spheroidal or "cuboidal" epithelium; *e*, acinus lined by hypertrophic or "columnar" epithelium. In the lower portion of the diagram is the relative size of the normal thyroid gland.

Anatomic Description

In figure 1, *A** represents thyroid shaped goiter. 1. Hypertrophic* simple or colloid goiter (*Ad*) is one in which there is a symmetric hypertrophy of the whole gland. The acini are dilated or enlarged, lined by low cuboidal cells, and contain colloid. In some of such goiters one also finds fetal and normal acini (*a, b, c*). 2. Hypertrophic parenchymatous goiter (*Ae*) is one in which there is symmetric hypertrophy of the whole gland. The acini are lined by columnar cells and may or may not contain colloid. They may vary greatly in size. All or some of the acini give evidence of parenchymatous hypertrophy. There may be some acini of the fetal (*a, b*), normal (*c*) and dilated type (*d*).

In figure 1, *B* represents nodular goiter. Hypertrophic nodular goiters are due to the presence of spheroidal circumscribed masses which usually can be shelled out. They vary in size; they may be microscopic or many centimeters in diameter. The spheroidal masses (adenomas**) are primarily composed of fetal acini (*b*) usually separated by loose connective tissue. There may be present others of the different types of acini (*a, c, d*) and in very rare instances acini with hypertrophic cells (*e*). Usually these spheroidal masses show signs of degeneration, which is the result of hemorrhage which destroys the tissues. Such hemorrhagic portions vary in size from petechial points to that in which the whole mass is involved. Such a mass may, therefore, be a cyst containing a hemorrhagic fluid and, in some instances, a brownish clear fluid containing crystals of cholesterol, depending on the length of time since the initial hemorrhage and destruction. In some instances, when the hemorrhage has been small, the region of destruction undergoes repair, and is filled in with scar tissue which sometimes becomes calcified. Small hemorrhagic portions often appear as yellowish spots, this being due to the presence of fatty degeneration of the cells to which the circulation has been impaired. Sometimes the spots are dark blue or purplish-blue, due to an early stage of disintegration of extravasated hemoglobin.

The glandular tissue surrounding the spheroidal masses may present any of the acini seen in the hypertrophic thyroid shaped goiters (figure 1, *A*). An anatomic classification follows:

*Much confusion arises even in the purest science from lack of definition of terminology. In this paper the term "hypertrophy" whenever used means increase of size, that is, a hypertrophic thyroid gland signifies only that the thyroid gland is enlarged above the normal size. The term applied to cells means the cells are enlarged.

**The term adenoma is usually applied to masses because they are circumscribed and composed of newly formed glandular tissues. Some confusion in the literature has occurred because of disputes over whether this newly formed tissue is circumscribed or not. As a matter of fact it usually is but one does find areas in some thyroid glands (particularly pathologic) which are not circumscribed. This is particularly true of the rare thyroiditis. It seems that the discussion is without practical importance and serves merely to confuse working knowledge.

A. (Thyroid shaped)
- Hypertrophic colloid goiters
- Hypertrophic parenchymatous goiters
- Atrophic parenchymatous goiters

B. (Nodular)
- Adenomatous goiters without parenchymatous hypertrophy
- Adenomatous goiters with parenchymatous hypertrophy
  - intra-adenomatous
  - extra-adenomatous
- Adenomatous goiters with parenchymatous atrophy
  - intra-adenomatous
  - extra-adenomatous

C. Thyroiditis
- acute
  - nontuberculous
- chronic
  - tuberculous

D. Malignancy
- carcinoma
- sarcoma
- epithelioma

(usually in degenerating adenomas)

E. Accessory thyroid tissue

The relative frequency of pathologic conditions of the thyroid gland is as follows:

	Specimens	
Hypertrophic colloid goiter (figure 1, *Ad*)	800	(2.4 per cent)
Hypertrophic parenchymatous goiter (figure 1, *Ae*)	9,520	(29.3 per cent)
Hypertrophic nodular goiters (figure 1, *B*)	21,787	(67 per cent)
Without parenchymatous hypertrophy (figure 1, *Be*) 18,444 (84.6 per cent)		
With parenchymatous hypertrophy (figure 1, *Bc*) 3,343 (15.4 per cent)		
Carcinoma	267	(0.8 per cent)
Sarcoma	7	
Epithelioma	7	
Tuberculosis	22	
Undifferentiated thyroid gland (figure 1, *a*)	58	
Hypertrophic fetal thyroid gland	1	
Total number resected thyroid glands (1911-1930 inclusive)	32,479	

Clinical Correlation

Enlargement of the thyroid gland of any type, especially when part of it is substernal, is frequently associated with symptoms and signs of pressure on the respiratory and circulatory apparatus.

The clinical syndrome known as hyperthyroidism, and frequently spoken of as a toxic condition, is associated with parenchymatous hypertrophy regardless of whether the goiter is thyroid shaped or nodular. After the administration of iodine, the parenchymatous hypertrophy usually disappears, although some or all of the symptoms and signs may remain. Thus, a goiter which previous to the administration of iodine may give evidence of typical parenchymatous hypertrophy presents itself as a hypertrophic colloid goiter after the administration of iodine.

Parenchymatous atrophy is associated with hypothyroidism, which manifests itself in two forms, cretinism and myxedema, and these conditions may occur in thyroid shaped thyroid glands or goiters, or in nodular goiters. In fact, a clinical condition of hypothy-

roidism is sometimes found even in the presence of parenchymatous hypertrophy. Thus, a cretin's thyroid gland may present the histologic picture of typical exophthalmic goiter. There is apparently a quantitative as well as qualitative relationship between parenchymatous hypertrophy and the clinical syndromes of hyperthyroidism and hypothyroidism.

As a result of these generalizations, the clinician may visualize and palpate the neck, determine if possible the form of the enlarged thyroid gland, decide whether it is thyroid shaped or nodular, and then determine whether the patient has or has not signs and symptoms of hyperthyroidism, hypothyroidism or pressure, and correlate their presence or absence with the diagrams (figure 1). Thus, in a very high percentage of instances, he should be able to forecast the gross and histologic pathologic characteristics. There will be a small error because even a thyroid shaped gland may con-

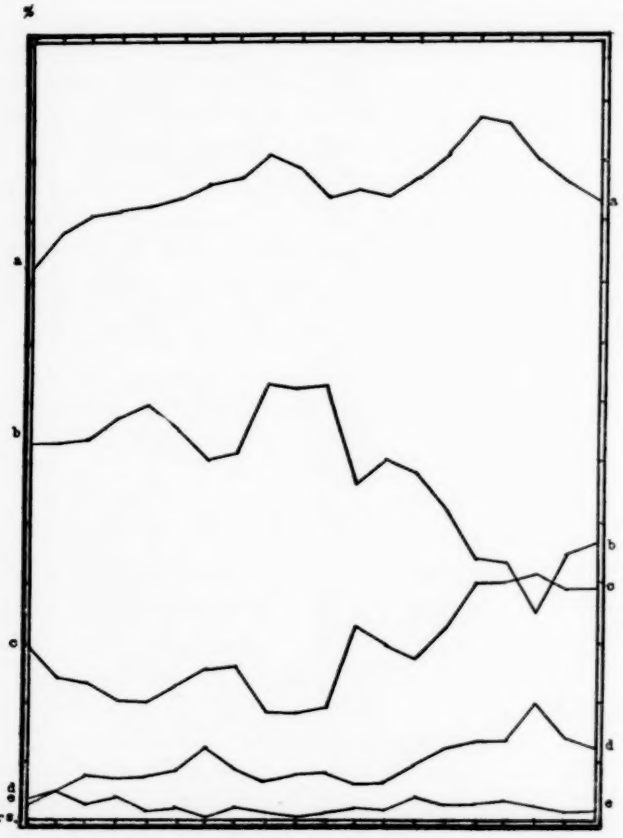

FIG. 2. Relative frequency of parenchymatous hypertrophy in goiters from 1911 to 1930 inclusive; *aa*, number of resected goiters; *bb*, percentage of simple nodular goiters without parenchymatous hypertrophy; *cc*, percentage of simple hypertrophic goiters with parenchymatous hypertrophy; *dd*, percentage of nodular goiters with parenchymatous hypertrophy; *ee*, percentage of simple hypertrophic colloid goiters.

tain a small impalpable adenoma. There is also the possibility that hyperthyroidism or hypothyroidism may not be sufficiently marked to be recognized clinically. Again, it is possible occasionally to mistake other obscure toxic conditions for hyperthyroidism.

It is of interest, and may be of future importance to note, that during this study over a period of twenty years (1911 to 1930 inclusive), there have been some variations in the relative frequency of the presence of parenchymatous hypertrophy, both in the thyroid shaped goiters and the nodular goiters. Figure 2 shows the percentage of hypertrophic colloid goiters, hypertrophic parenchymatous goiters, and parenchymatous hypertrophy in nodular goiters. Thus, there is an apparent increase in the presence of parenchymatous hypertrophy in both groups of goiters, beginning about 1921. The studies during the whole period of twenty years were made under the guidance of the same staff, and although acuity of vision might have increased with experience it does not seem that the variation should be quite so pronounced. This increase suggests, as H. S. Plummer[3] has frequently pointed out, that there might be epidemics of hyperthyroidism. Further regional studies are being made to substantiate or refute this possibility.

It is the object of this short review of a very large amount of material to give the active practicing clinician the fundamental universal facts which have so frequently been confused by elaborate discussions, dissertations, articles, and monographs on the subject of goiter.

BIBLIOGRAPHY

[1]Boothby, W. M.: The thyroid problem. Collected Papers of Mayo Clinic, 1928, xx, 495-515.

[2]MacCarty, W. C.: Goiter and its relation to its structural and physiological units, Surg., Gynec., and Obst., 1913, xvi, 406-411.

[3]Plummer, H. S.: Personal communication.

The Heart in Hyperthyroidism*†

By Henry M. Thomas, Jr., *Baltimore, Md.*

In discussing the heart in hyperthyroidism I shall try to take up clinical points about which there has been much controversy in the past. In order to establish a proper background I shall briefly summarize the history of this subject.

In the first allusion to hyperthyroidism made by Parry[1] in 1786 (and published posthumously in 1825) eight cases of a peculiar heart disease, attended by exophthalmos and thyroid enlargement were described. He evidently considered the disease primarily a cardiac affection with secondary exophthalmos and enlargement of the thyroid gland. Although Adleman[2] in 1829 spoke of "Kropfherz," the Englishmen, Graves,[3] Stokes,[4] Marsh[5] and McDonnel,[6] who seem to have written separately between 1840 and 1855 about the same group of cases, still thought the enlargement of the thyroid gland and the exophthalmos came after the heart trouble. In this country Markham,[7] in 1858, reported "affection of the heart with enlarged thyroid and thymus glands and prominence of the eyes." Moebius[8] and later Horsley[9] and Kocher[10] and Müller[11] recognized the part played in the syndrome by the thyroid, but an accurate conception of the heart changes was far from being elaborated at that time. The surgeon, Rose,[12] working at Zurich, wrote a long paper in 1877 pointing out the importance of considering the heart in operations on the thyroid gland. He thought that the goiter compressed the trachea and thus, by interfering with the breathing, placed the right heart under strain. His method of treatment was to perform a preliminary tracheotomy to relieve the heart of this particular form of strain. Thus the so-called goiter heart of Rose was a heart enlarged and weakened purely by a mechanical obstruction. Many other writers noticed decompensation of the heart in patients with large goiters. These observations were practically all made in the goiter regions in Switzerland, the Tyrol, Bavaria, etc., by Wolfler,[13] Wette,[14] Thomas, Schranz[15] and others. Finally Kraus,[16] in 1899, brought forth his conception of the so-called neurotic or thyrotoxic heart. His view has been generally accepted although there is still some confusion about those cardiac conditions which occur in patients with goiters which are obviously not toxic. I allude to such frank cases as the heart in cretins with goiters, etc. It is likely that the authors from goiter districts

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are describing cases of myxedema heart without clearly differentiating them from hyperthyroid heart. Even as late as 1926, European writers (Meyer and Sulger,[17] and Andrassy) have considered the cardiac disturbances in goiter due to pressure on the trachea, the great vessels, or the vagus and sympathetic nerves of the neck.

In America we have come to a fairly clear differentiation between hyperthyroid heart and myxedema heart and most of us still maintain open minds as to the occasional occurrence of a purely mechanical thyroid heart. Of these three forms of thyroid heart disease, by far the most common is the one associated with hyperthyroidism, and, therefore, I shall limit my discussion to this variety. We do not believe that there is any essential difference between hyperthyroidism from a nodular goiter and that from the diffuse goiter of Graves' disease. The fact that a nodular goiter may exist for a long time before cardiac symptoms develop has led some people to believe that nodular goiter may damage the heart. We have seen no proof of this and are inclined rather to believe that a mild degree of hyperthyroidism which has existed for some years finally becomes evident when the cardiac reserve has been diminished.

If I may state the conclusion at the outset of my discussion, I can then build up the full clinical picture in what I think is its logical sequence. This conclusion is:

The primary effect of hyperthyroidism on the circulatory system is tachycardia. This tachycardia is effected in several ways:

(a) By additional work associated with an increase in blood flow caused by the elevated body metabolism;

(b) By stimulation of the accelerator fibers of the sympathetic nervous system;

(c) By direct action of an excess of thyroxin on the heart muscle cells.

I can not substantiate with experimental data the statement that the heart rate goes up in response to an elevated metabolic rate. Some years ago Sturgis[18] pointed out that the increase in heart rate paralleled the elevation in the metabolic rate. But it is perfectly obvious that the same factor which had an effect on the metabolism might quite independently have an effect on the heart rate. In this connection it is interesting to consider the effect of thyroid medication on cases of heart block. Willius,[19] and Aub and Stern[20] have reported the results of such treatment and we have had one case in our clinic. Briefly, the ventricular rate is unaffected by large doses of thyroxin although the metabolism goes up and the blood flow increases; the auricular rate, on the other hand, which is still under the control of the vagus and accelerator nerves, increases from 70 to 120. I do not believe that any final conclusions can be drawn from these facts, and I am under the impression that most observers believe that the usual response to the increased blood flow is an increased heart rate. There are various indications of the effect of the accelerator fibers on the tachycardia of hyperthyroidism. Ergotamine has been used to block the accelerator impulses and in some cases a slowing of the heart rate has been accomplished. The over-activity of the sympathetic sys-

tem in other ways has been given as circumstantial evidence of over-activity of the accelerator fibers. But the effect of thyroxin on the heart muscle itself has been clearly demonstrated by Lewis and McEachern.[21] Experiments with isolated hearts from animals which have been rendered hyperthyroid by feeding with thyroid extract show that these heart muscle preparations maintain a rapid rate of contraction (26 to 144 beats per minute faster than normal preparations under the same conditions) for as long as ten hours, the longest period over which they have been observed as yet. This suggests an increase in the heart muscle cell metabolism.

Now, as the hyperthyroid tachycardia persists, however it may have been produced, the rest of the signs and symptoms of thyroid heart gradually come into the picture. If the patient is a young, healthy individual, his heart will be able to stand even an excessive degree of hyperthyroidism without evidence of congestive heart failure. If he is past middle age and his heart therefore is out of training and unused to the excessive strain which the constant running around of young individuals produces; or, on the other hand, his heart is the site of valvular or arteriosclerotic heart disease with diminished cardiac reserve, then, sooner or later, congestive heart failure will occur. In practically every instance this is associated with, or preceded by, auricular fibrillation. It is not clearly known whether auricular fibrillation is purely a failure of the auricles to respond to too much work or whether thyroxin adds a degree of irritability to the muscle fibers which causes them to fibrillate sooner than otherwise. The fact that young, healthy hearts rarely fibrillate even under the most severe degree of hyperthyroidism lends weight to the idea that it is purely an over-work phenomenon which occurs only when the cardiac reserve has been overdrawn. Seven and a half percent of the cases of auricular fibrillation recorded in the Heart Station of the Johns Hopkins Hospital were patients suffering from hyperthyroidism (McEachern).

Among the cases which develop auricular fibrillation some do not show signs of congestive heart failure. Hamilton[22] has stressed this point and carefully described the clinical picture of those with congestive failure. He points out that in his series of 50 such cases, exophthalmos was usually absent, the thyroid gland was often normal in size, the tremor and nervousness almost never occurred. In recognizing this condition from the other causes of congestive heart failure, he stresses (a) tachycardia which does not respond as well as would be expected to complete rest and digitalization, (b) history of unexplained loss of about 30 pounds, (c) history of a surprisingly long duration of complete disability associated with gross signs of heart failure, (d) elevated BMR (he states that non-thyrotoxic congestive heart failure cases may have a BMR of +64 which will return to normal when the heart failure is relieved). The average age of this series of Hamilton's cases was 50 years. One might suppose that this group (like many cases of so-called toxic adenoma) is comprised of patients whose cardiovascular systems were damaged to a

degree whereby slight hyperthyroidism (so slight that the characteristic clinical signs of exophthalmos, goiter, tremor and restlessness are hardly noticeable) could cause myocardial insufficiency. This series of Hamilton's brings out the fact more clearly that when congestive heart failure occurs in hyperthyroidism, the failure is brought about, not by excessive hyperthyroidism, but by moderate or slight hyperthyroidism superimposed on an inferior cardiovascular system.

Whether or not dilatation and hypertrophy occur in uncomplicated thyroid heart is still an unsettled question. Those who think that hypertrophy of the ventricles occurs can find confirmation in the experiments on laboratory animals. Cameron and Carmicheal[23] in 1921 produced hypertrophy of the heart in rats by feeding thyroid extract. Last year Simonds and Brandes[24] reported their work on dogs. They found that the hypertrophy involved all the chambers of the heart with a slightly greater proportional increase in the left ventricle. Also most accounts of the postmortem findings of the thyroid heart describe hypertrophy in a large number of the cases and of 27 thyroid hearts studied in the Pathological Department of the Johns Hopkins Hospital by McEachern and Rake,[25] 16 had definite hypertrophy. Lewis[26] reported 12 cases, in all but three of which the heart weighed over 300 grams. Means and Richardson[27] also have reported the necropsy findings in 12 cases. Their series showed but little hypertrophy. The clinical evidence is not clear cut. Hurxthal[28] made careful cardiac measurements on thyroid patients before and three months after operation. He found no contraction in the size of the heart, from which he inferred that there had been no previous enlargement. He further compared 100 cases of toxic goiter with 100 cases of non-toxic goiter and, after making correction for the transverse diameter of the chest and body weight, he concluded that the average transverse diameter of the heart in the toxic group exceeded that of the non-toxic group by only 0.49 cm. It seems likely to us that the hypertrophy has occurred only as a result of a well marked and fairly profound hyperthyroidism. We can say definitely that when congestive heart failure occurs dilatation of the ventricles is very likely to be found and this dilatation disappears entirely when the hyperthyroidism has been removed.

The blood pressure shows a slight elevation in the systolic pressure and diminution in the diastolic pressure. If a pronounced degree of hypertension is encountered it is likely that this condition will persist or become worse after operation. The electrocardiogram shows an unusually prominent T wave and Hamberger[29] has noted a parallel in the degrees in basal metabolic rate and the height of the T wave following iodine medication and thyroidectomy.

If the hyperthyroidism is successfully terminated by subtotal thyroidectomy and adequate post-operative treatment is observed, the heart will, sooner or later, return to the state in which it was found at the beginning of the hyperthyroidism, allowing only for changes which would have occurred in a similar length of time under other

conditions. This statement is a brave one. Let me show a condensed chart of such a patient.[30] (See chart 1).

Careful search for pathological changes in the hearts of patients dying from hyperthyroidism has yielded very inadequate findings. Various reports have been made noting changes in the heart muscle and these reach their high point with Goodpasture's[31] account of two cases which showed degeneration and necrosis of the heart muscle fibers. Current opinion is that patients dying from thyrotoxic heart failure show a variety of inconstant minor lesions, none of which can surely be ascribed to hyperthyroidism. Some of the changes described are cardiac dilatation and hypertrophy, slight round cell infiltration and hyaline and fatty degeneration of the muscle fibers. An exhaustive examination of all the hearts of patients dying with hyperthyroidism at the Johns Hopkins Hospital has recently been made by McEachern and Rake.[25] This work is soon to be published in a monograph form. Stated briefly their conclusions are that no pronounced pathological change is produced in the heart by hyperthyroidism.

If you will accept the foregoing

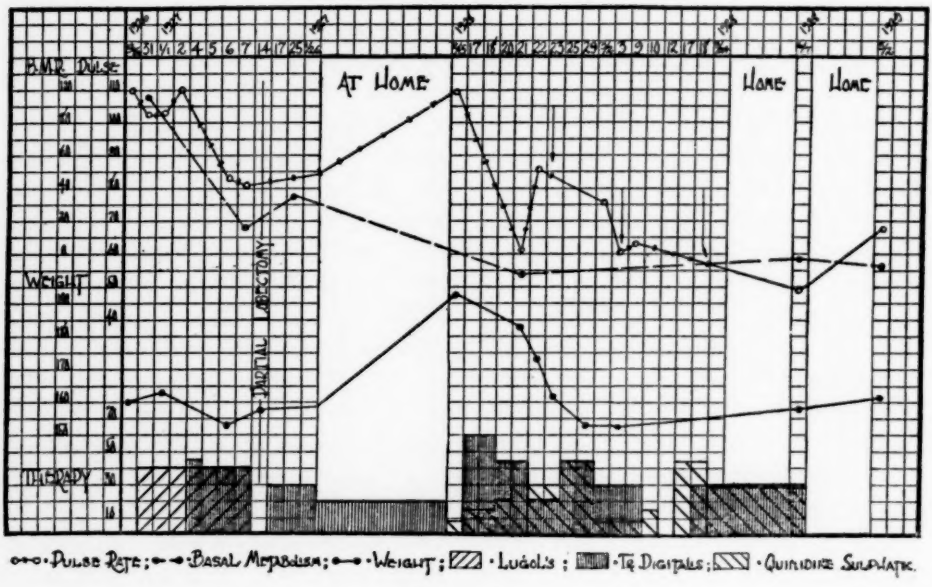

CHART I.

Following the partial lobectomy the patient insisted on returning home before the auricular fibrillation had been interrupted. During the 13 months at home on digitalis, under the direction of his local physician, he continued to fibrillate and gradually went down hill. During his second stay at the hospital on rest, digitalis and quinidine, he excreted 33 pounds of fluid in 8 days and reverted to normal rhythm on the 8th day. Since September 12, 1928, he has done full manual labor as a track man on the railroad without the loss of a single day from sickness and without taking either digitalis or quinidine. (This chart was drawn by Mr. Charles McCurdy Gray, a member of the graduating class of the Johns Hopkins Medical School. Reprint from Bulletin of the Johns Hopkins Hospital, 1930, xlvii, 1-10).

hypothesis of the heart in hyperthyroidism the road to proper treatment will be quite clear. The first principle is that until congestive failure occurs no specific treatment for the heart is indicated; the second principle is that when once congestive heart failure has occurred it should be treated like any other form of congestive heart failure. I should like to make one exception to this statement and warn against the pre-operative use of quinidine for auricular fibrillation. The reason for this is that in the face of hyperthyroidism a fibrillating heart can be better controlled by digitalis than a heart with a regular mechanism. For example the ventricular rate of a case of auricular fibrillation in hyperthyroidism can be slowed under digitalis to 70 or 80 or 90 beats to the minute and the circulation greatly improved in this way. If, then, this digitalized heart is made to revert to normal mechanism by quinidine the slowing effect of digitalis may be lost and the rate suddenly jump up to 160 or 180. I have seen one such case in which just such a change took place, followed in the course of a few hours by exitus. When suitable therapeutic measures have been applied for relief of the heart failure the more important treatment of the hyperthyroidism can be undertaken. One must not be too cautious as to surgical procedures in cases of this kind as they are surprisingly well borne by these patients and they alone offer permanent relief.

Friedrich Müller and others have made the statement that iodine occasionally has a deleterious effect on the heart muscle. Laboratory animals have been given relatively enormous doses of iodine with the production of slight pathological changes in the heart muscle, noticeable by microscopic examination. In the Johns Hopkins Cardiographic Laboratory a number of observations have been made on normal individuals before and after taking large doses of Lugol's solution[32,33]. No changes were found in the electrocardiographic tracings or in other heart examinations in this series despite the fact that several of the individuals proved to be hypersensitive to iodine and suffered from varying degrees of skin eruptions and gastro-intestinal upsets. Dr. John T. King, Jr.,[34] observed a case of an elderly woman suffering from nodular goiter with hyperthyroidism. After four days of rest in bed and Lugol's solution, ten minims three times a day, her heart rate became absolutely irregular. The Lugol's solution was discontinued and, in three days, the heart returned to normal rhythm. Of course this one case is not conclusive, but it illustrates very well my feeling in this matter. I believe that to a thyrotoxic heart iodine may be the additional factor which causes the final break. It seems quite likely to me that most of the cases of so-called iodine hyperthyroidism (Jod-Basedow) are in reality iodinism superimposed on hyperthyroidism.

We finally may conclude that the heart, like the rest of the body, responds to hyperthyroidism by being speeded up. Given a normal young cardiovascular system, this speeding up is a matter of little or no consequence. On the other hand, given a heart which is weakened by advancing age or heart disease and then the constant accelera-

tion from hyperthyroidism frequently leads to congestive heart failure. In either instance removal of the hyperthyroidism allows the heart to regain, both functionally and structurally, its pre-hyperthyroid condition.

I wish to express my indebtedness for criticism and suggestions during the preparation of this paper, to Dr. Donald McEachern of the Johns Hopkins Hospital Medical House Staff, whose original work and whose familiarity with the literature on this subject made his help of great value.

BIBLIOGRAPHY

[1]Parry, C. H.: Collections from the unpublished writings of the late C. H. Parry, Underwood, London, 1825.

[2]Adlemann, G.: Beiträge zur Pathologie des Herzens, der Schilddruse und des Gehirns, Jahrbucher der Philosophisch-Medizinischen Gesellshaft zu Wurzburg, 1928, i, 104-108.

[3]Graves, R. J.: Clinical Lectures, Lond. Med. and Surg. Jr. (Renshaw's), 1835, vii, 516. Also: Clinical Lectures delivered during the Sessions of 1834-5 and 1836-7, Philadelphia, 1838.

[4]Stokes, W.: Diseases of the heart and the aorta. Dublin, 1854, p. 278.

[5]Marsh, Sir Henry: Dilatation of the cavities of the heart—Enlargement of the thyroid gland, The Dublin Jr. of Med. Sci., 1841, xx, 471.

[6]McDonnel, J. D.: Observations on a peculiar form of disease of the heart, attended with enlargement of the thyroid gland and eyeball, Dublin Jr. of Med. Sci., 1845, xxxvii, 200.

[7]Markham, W. O.: Affection of the heart, with enlargement of thyroid and thymus gland, and prominence of the eyes, Trans. Path. Soc., London, 1857, ix, 163.

[8]Moebius, P. J.: Über insufficienz der Konvergenz bei Morbus Basedowii, Centralbl. f. Nervenh, 1886, ix, 356. Also: Die Basedow'sche Krankheit, Vienna, Ed. 2. H. Holder, 1906.

[9]Horsley, Sir V.: The thyroid gland; its relation to the pathology of myxedema and cretinism, to the question of the surgical treatment of goitre, and the general nutrition of the body, Brit. Med. Jr., 1885, i, 111.

[10]Kocher, T.: Über Kropfexstirpation und ihre Folgen, Arch. f. klin. Chir., 1883, xxix, 254.

[11]Müller, F.: Beiträge zur Kenntniss der Basedow'schen Krankheit, Deutsch. Arch. f. klin. Med., 1893, li, 335.

[12]Rose, E.: Über den Kropftod und die Radicalcur der Kropfe, Arch. f. klin. Chir., 1878, xxii, 1.

[13]Wolfler, A.: Zur chirurgischen Anatomie und Pathologie des Kropfes und Nebenkropfes, Arch. f. klin. Chirurgie, 1890, xl, 346-428.

[14]Wette, Theodore I.: Beiträge zur Symptomatologie und chururgischen Behandlung des Kropfes., Arch. f. klin. Chirurgie, 1892, xliv, 652-716.

[15]Schranz, Julius: Beiträge zur Theorie des Kropfes, Arch. f. klin. Chirurgie, 1886-87, xxxiv, 92-159.

[16]Kraus, F.: Über Kropfherz; Besiehungen zwischen Struma und Morb. Basedowii, Wien. klin. Wchnschr., 1899, xii, 416.

[17]Meyer, A. W., and Sulger, E.: Goiter heart before and after operation, Med. Klin., 1926, xxii, 838-840. (Abst.) Jr. Am. Med. Assoc., 1926, lxxxvii, 372.

[18]Sturgis, C. C., and Tompkins, E. H.: A study of the correlation of the basal metabolism and pulse rate with hyperthyroidism, Arch. Int. Med., 1920, xxvi, 467.

[19]Willius, F. A.: Heart in thyroid disease, Ann. Clin. Med., 1923, i, 269.

[20]Aub, J. C., and Stern, N. S.: The influence of large doses of thyroid extract on the total metabolism and heart in a case of heart block, Arch. Int. Med., 1918, xxi, 130.

[21]Lewis, J. K., and McEachern, D.: Persistence of accelerated rate in isolated hearts and auricles from thyrotoxic rabbits; response to iodides, thyroxin and epinephrin. Johns Hopkins Hospital Bull., in press.

[22]HAMILTON, B. E.: Heart failure of congestive type caused by hyperthyroidism, Jr. Am. Med. Assoc., 1924, lxxxiii, 405-410.

[23]CAMERON, A. T., and CARMICHAEL, J.: Comparative effects of parathyroid and thyroid feeding on growth and organ hypertrophy in white rats, Am. Jr. Physiol., 1921, lviii, 1.

[24]SIMONDS, J. P., and BRANDES, W. W.: Size of heart in experimental hyperthyroidism, Arch. Int. Med., 1930, xlv, 503-512.

[25]MCEACHERN, D. and RAKE, G.: A study of the morbid anatomy of hearts from patients dying with hyperthyroidism. Johns Hopkins Hosp. Bull., 1931, xlvii, 273.

[26]LEWIS, WILLIAM: Hyperthyroidism and associated pathology, Am. Jr. Med. Sci., 1931, clxxxi, 65.

[27]MEANS, JAMES H., and RICHARDSON, EDWARD: Diseases of the thyroid. Oxford Monographs on Diagnosis and Treatment, 1929, Oxford University Press, New York.

[28]HURXTHAL, LEWIS N.: The cardiovascular system in goiter, Tr. Am. Assoc. for the Study of Goiter, 1930, Portland, Ore.

[29]HAMBERGER, W. W.; LEVY, M. W.; PRIEST, W. S., and HOWARD, HELEN C.: The heart in thyroid disease, Arch. Int. Med., 1929, xliii, 35-49.

[30]THOMAS, HENRY M., Jr.: Thyroid heart; a transitory condition, Johns Hopkins Hosp. Bull., 1930, xlvii, 1-10.

[31]GOODPASTURE, E. W.: Myocardial necrosis in hyperthyroidism, Jr. Am. Med. Assoc., 1921, lxxvi, 1545-1551. Also: Myocardial necrosis, Jr. Exp. Med., 1921, xxxiv, 407.

[32]MCEACHERN, D.: The effect of the ingestion of potassium iodide on the pulse rate of normal individuals, Johns Hopkins Hosp. Bull., 1930, xlvii, 299-303.

[33]MCEACHERN, D., and BAKER, B. M.: The effect of the ingestion of potassium iodide on the electrocardiogram of normal individuals, Johns Hopkins Hosp. Bull., 1930, xlvii, 304.

[34]KING, JOHN T., Jr.: Personal communication.

Medical Aspects of Peptic Ulcer*

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IT is almost necessary to make an excuse for writing about peptic ulcer. Medical literature of the past twenty years has been filled with articles on this subject, volumes have been written about it and a verbal war between the advocates of medical and surgical treatment is still being waged with great intensity. When so much verbiage is wasted on any subject it engenders the suspicion that the reason for this wastage is a lack of knowledge or understanding of the subject. In the case of ulcer this is undoubtedly true. So much good research work has been done in regard to the pathology and etiology of ulcer and so well have the findings agreed with clinical experience, that it is surprising to hear even prominent surgeons and clinicians say that the cause is unknown. It is also peculiar that with the multiplicity of articles dealing with the well-known fact that in peptic ulcer there are almost invariably evidences of other inflammatory changes in stomach, duodenum, biliary tract, liver, pancreas, small and large intestine and appendix, it is taking both clinicians and surgeons so long to realize that in considering peptic ulcer as an entity and treating it as such they are not only illogical, but are definitely to blame for the poor results so generally reported.

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Pathology

The pathology of peptic ulcer has not been given the attention it deserves. Lewis Gregory Cole has made a very valuable contribution to our knowledge in his studies of freshly excised ulcers, and parts of stomachs with ulcers, during the past five or six years, and his findings should be more generally made known. Cole divides ulcers into three groups, those of the body of the stomach, "corporic ulcers," those of the prepyloric region, "prepyloric or pyloric ulcers," and those of the first portion of the duodenum, "postpyloric ulcers" or "ulcers of the cap." He has shown that the ulcers are not the result of an erosion of the mucosa, but that they begin as areas of focal necrosis in the stomach or duodenal wall, and that they burst through in the line of least resistance, just as carbuncles or boils break through the skin. The intact mucosa can be seen curled under the edge of the ulcer. The size and depth of the ulcer depend on the site of the original area of focal necrosis and the degree of elasticity of the wall at this point. Thus an area of focal necrosis just under the mucosa breaks through rapidly and produces the small, rapidly healing submucosal ulcer, practically no more than a "canker sore," usually found in the prepyloric region, where there is little opportunity for its spread due

to a relatively inelastic wall. An area of necrosis in the deeper layers, especially if in the loose areolar area along the lesser curvature of the stomach, will produce a deeper, wider ulcer. If the area is under the serosa, perforation is liable to result. All ulcers have a remarkable tendency to heal, as shown microscopically by evidences of a reparative process at the base of the ulcers, and as Cole has demonstrated in the living stomach by repeated serial roentgenograms, at short intervals, showing prepyloric ulcers disappearing in from a few days to two weeks and large lesser curvature ulcers in from a few weeks to two or three months. The healing of duodenal ulcers, because of the frequently persistent deformity resulting, is not as clearly demonstrable by radiography, but can be shown by reduced irritability of the duodenum on fluoroscopy and by disappearance from the duodenal contents of the ulcer base slough and blood. By demonstrating in removed stomachs the presence of multiple microscopic ulcer scars, often dozens in one stomach, Cole has arrived at the inevitable conclusion that each recurrent attack of ulcer symptoms is due to a new ulcer and that symptoms persisting or perhaps varying in intensity, are due to new ulcers developing before the older, partially healed ones have ceased to cause symptoms. Contrary to previously conceived notions, the finding of two or more ulcers in various stages of healing, is not at all unusual.

The *complications* of ulcers are easy to understand. *Perforation* has already been mentioned, and has for many years been considered not a breaking through of an old ulcer, but a separate disease, the occurrence of such a severe ulcer that it immediately punched a hole through the whole stomach wall. Cole's explanation of this type of ulcer as due to an area of focal necrosis just under the serosa and breaking through in both directions, is simple and clear. If the point of perforation is opposite some organ, like liver or pancreas, or if it occurs into the lesser peritoneal sac, only a localized well-walled-off abscess area may result, but frequently the break occurs into the general peritoneal cavity, with resulting general peritonitis.

In the case of large or deep ulcers, especially where these are located at a narrow point, like pylorus or duodenum, although occasionally also in mid-lesser curvature, healing or external inflammatory reaction or both may result in so much cicatrical contraction as to cause obstruction to the onward passage of food—*pyloric stenosis* or *hour-glass constriction.* Acute inflammatory changes at such an area of narrowing or in a large ulcer may at times cause temporary complete stenosis, which may become partial or may disappear as the edema subsides.

Gross hemorrhage from ulcer is comparatively rare, and is due to the fact that the area of necrosis producing the ulcer happened to involve one of the larger vessels of the stomach wall. Hemorrhage will recur until the damage is repaired—usually by the organization of a thrombus in the injured vessel. If the eroded vessel is one running at right angles to the base of the ulcer (a terminal vessel) prompt retraction and cessation of hemorrhage occur; if lying longitudinally, with ero-

sion of its side wall, the hemorrhage will be persistent and often fatal. The vessels of some individuals seem less resistant to infection and these individuals tend to have hemorrhages with each recurrent ulcer. Superficial bleeding and serous exudation occur during part of the cycle of all ulcers.

The possibility of *carcinomatous degeneration* of gastric ulcers has in the past few years been relegated to its proper status. Studies conducted all over the world, and based on both clinical observation and pathological findings, have shown that carcinoma is no more apt to occur in the stomach of an ulcer patient than in the normal stomach, carcinoma having been shown to occur at the most in but four per cent of such cases. Cole, ten years ago, showed by statistics of cases seen by him that gastric carcinoma occurred more frequently in patients who had had operations for ulcer than in those treated medically. If we are to accept Cole's findings, which indicate spontaneous, rapid and complete healing of ulcers, it would give but little time for the development of malignant changes in any given active ulcer, leaving only the scar to act as a nidus.

Etiology

The etiology of ulcer has been another moot point. The older theories considering trauma or irritation as etiologic factors were suddenly confronted, more than sixteen years ago, by Rosenow's demonstration of the etiologic relationship between focal infection and ulcer. Although Rosenow's laboratory experiments have not been universally confirmed by other observers, probably due to their using a different technique, the clinical experience of those who have, like myself, made the removal of all possible focal infections the *sine qua non* in treatment, has been such as amply to substantiate the claims of such a relationship. Previous to Rosenow's experiments, Fenton B. Turck, showing that areas of focal necrosis could be produced in animals by intravenous injection of solutions of dead tissue (which contain minute amounts of the destructive shock toxin he has named cytolysin), in some instances produced typical indurated gastric ulcers in a few minutes. He concluded that this cytolysin was the causative factor. It seems only reasonable to assume that what may occur at the site of a focal infection, is an absorption of the cytolysin produced in the dead tissue resulting from the infection, and that the secondary focal necroses may be due more to electrochemical reactions of the tissues to this cytolysin than to actual initial migration of bacteria to the intact stomach wall. On the other hand, what relation anaphylaxis due to bacterial or tissue sensitization bears to the problem, has not as yet been satisfactorily determined. However, the results obtained in preventing recurrent ulcer when all possible infective foci have been removed, and the repeated recurrences in spite of any medical or surgical treatment where these foci have been neglected, affords clinical proof of the etiologic relationship between the foci and the ulcers.

Pathological Physiology

The *disturbed function* caused by the presence of an ulcer in stomach or duodenum is due primarily to irrita-

tion, and the results will vary with the degree of irritability of the patient's stomach, his general nervous irritability and the severity of the usually concomitant lesions in other parts of the gastrointestinal tract and its appendages. The most common result of irritation on the *motor function* of the stomach is an increase in the frequency and severity of the normal hunger contractions of the empty stomach, and at times the occurrence of such contractions before the stomach is entirely empty. Also, especially when an ulcer is near the pylorus or beyond it, there is frequently intermittent pylorospasm. In duodenal ulcer, and more particularly in lesions further down in the gastrointestinal tract, retroperistaltic waves (the retrostalsis described by Alvarez) may produce troublesome symptoms.

The effect of ulcer on the *secretory function* of the stomach is to cause an increased irritability of the gastric glands, with a resulting continued secretion, often reaching high levels of acidity, although at times there may be diminution or even an absence of hydrochloric acid in the gastric contents, due either to the exhausting effect of prolonged irritation or to chronic inflammatory changes, involving the gastric glands.

Symptomatology

The *symptoms* of peptic ulcer are in most cases very characteristic. Epigastric pain, occurring after a longer or shorter interval after eating (usually from one-half to four hours after meals) and promptly relieved by the intake of any food or drink—the "hunger pain" of Moynihan—is practically pathognomonic of ulcer. This pain is due to exaggeration of the normal hunger contractions of the empty stomach, and its severity and the time of its occurrence are, as mentioned above, dependent upon the irritability of the stomach and also upon the size and frequency of the meals taken, so that while some patients may get a severe pain within an hour after eating, others may feel no pain at all. The location of the ulcer has no effect upon the time pain will occur—gastric ulcers may cause pain three or four hours after meals, duodenal ulcers one or two hours after. If ulcers occurred alone, that is, if there were not, as there invariably is, an accompanying inflammatory reaction in other parts of the gastrointestinal tract, the symptoms would probably always be typical. These other conditions, the inflammations of the biliary tract, pancreas, appendix and colon, not only produce symptoms directly referable to themselves, but cause retrostaltic waves, producing pylorospasm and mild or severe reverse peristalsis in the stomach, resulting in epigastric distress or fulness immediately after meals, aerophagia, heartburn, sour eructations or actual regurgitation or vomiting. Some of them also cause more or less severe bowel symptoms. These other symptoms may be so prominent as to mask or modify the characteristic ulcer symptoms, thus making diagnosis by history alone very difficult. Loss of weight and strength, anemia, and various nervous manifestations are due to the individual patient's reaction to the symptoms—some starve themselves and grow thin and anemic, others overeat and gain weight rapidly. Some con-

sider that as long as food relieves them there is no cause for worry, others suspect cancer and become neurasthenics.

The *symptoms of the complications* of ulcer are rather characteristic. In *gross hemorrhage,* hematemesis and melena, usually preceded by severe pain and fainting or collapse, are typical, although in the absence of hematemesis, the characteristic sticky, tarry stools, passed during the night may not be noticed, and the patient may describe only a diarrheal attack with vertigo or syncope.

Perforation, ushered in by a terrific pain, not relieved by the food or alkali which the patient usually tries before the doctor arrives, and which is sooner or later followed by shock and the symptoms of peritoneal irritation, is a condition requiring immediate recognition so that prompt resort may be had to a life-saving operation.

Pyloric stenosis and *hour-glass constriction* present the characteristic symptoms of delayed vomiting, that is, vomiting occurring at an interval after meals when all foods should normally have been expelled from the stomach. Patients with this complication who may previously have vomited soon after eating or at the time of occurrence of the ulcer pain, begin to vomit less frequently, often in the evening, and in the vomitus may be recognized food eaten two or three meals previously or even from the day before. Frequently there is a diminution of the ulcer pains, but a feeling of fulness in the upper abdomen and a more or less marked anorexia.

The occurrence of *carcinomatous change* in an ulcer is accompanied by an unusual loss of weight and strength, and an increasing pallor, associated either with symptoms similar to those previously complained of or a new train of rather indefinite dyspeptic symptoms, with anorexia. Often gross hemorrhage may be the first symptom of a carcinoma.

Diagnosis

The diagnosis of peptic ulcer is usually made by means of three characteristic findings—the history, examination of gastric and duodenal contents by the fractional method and the roentgen ray examination.

1. The *history* is often of the greatest help in diagnosis. Recurrent attacks of typical hunger pain, that is, pain occurring after an interval of from one-half to three or four hours after meals and relieved by the intake of food, drink or alkali, was long ago described by Moynihan as pathognomonic of ulcer, and in my experience it is extremely uncommon not to be able to demonstrate an ulcer when this symptom is present. The pain is most commonly located in the epigastrium, but at times may be located in the gallbladder or appendix regions, in either inguinal region, the precordium or the back. Retrostaltic symptoms, as described above, are not characteristic of ulcer, but are more frequently due to the other co-existent gastrointestinal lesions. Vomiting, occurring immediately after meals or at the time of the pain, is one of these retrostaltic symptoms, but if it is of the "delayed" type, is characteristic of stenosis. The symptoms of other complications have been mentioned. A first attack of ulcer symptoms, especially in a patient

of carcinoma age and if continuing over a period of a few months, may be due to a carcinomatous ulcer.

2. Careful *fractional gastric analysis,* preceded by examination of the fasting residue after a duration meal of rice and raisins, is of great help in diagnosis. Three findings are studied: namely, those relating to motility, to secretion and to admixtures.

A. *Motility*: an overnight residue of gross rice and raisins indicates pyloric stenosis, the degree of which may be determined by the rapidity with which the stomach can expel the test meal subsequently given. In the absence of an overnight residue, delayed expulsion of the test meal indicates marked pylorospasm and the probable presence of a lesion near the pylorus, but not obstructing it.

B. *Secretion* is indicated by the curve of acidity following ingestion of a test meal or the intramuscular injection of histamine dihydrochloride. In gastric ulcer this curve is not of value: there may be a normal curve, there may be no secretion of acid at all or there may be a continued secretion. In pyloric and post-pyloric ulcers we find that a continued secretion, i.e., secretion continuing beyond the normal period of secretory reaction to a stimulus, and often reaching great heights of acidity, is the rule, although here, also, achylia is found at times, especially in long-continued cases.

C. *Admixtures.* The presence in the gastric contents of small, more or less dried particles of blood, with adherent detritus coming from the base of an ulcer, is a valuable finding, but is difficult to differentiate from blood due to trauma in swallowing the tube. It is, however, of some value in confirming an x-ray finding of gastric ulcer. Where no blood is found in the gastric contents until the normal reflux of bile stained duodenal contents during the second hour after the test meal, and the particles just described are then encountered, we have a very characteristic finding of duodenal ulcer. Gastric analysis is of little or no value in differentiating between gastric ulcer and even well-advanced carcinoma, although the continuous presence of blood is suspicious of malignancy. In rare instances pieces of carcinoma tissue may be aspirated and recognized microscopically. In carcinoma associated with pyloric stenosis, a fasting residue containing no free hydrochloric acid and in which Boas-Oppler bacilli and lactic acid are present, is found in a large proportion of cases.

3. The *roentgen ray diagnosis* of ulcer is of great importance. The characteristic findings on a radiographic film are the presence of a *defect,* which represents the displacement of the ingested barium mixture by the area of induration about an ulcer, and a *protrusion* (niche) which represents the crater of the ulcer. In the case of the large (corporic) ulcers which nearly always occur at some point along the lesser curvature, the protrusion may be large (up to 5 cm. in diameter) and the defect extensive. In the case of small prepyloric ulcers the protrusion may be very small, the defect barely noticeable. In the duodenal cap the crater is not as frequently seen, but the induration causes persistent deformities which are characteristic.

Fluoroscopic examination is subject to grave error in that more than fifty per cent of even large corporic ulcers are not recognized and the small prepyloric ulcers are rarely seen, although the deformity and irritability of the duodenum make ulcers of the cap easily recognizable by this method.

A persistent deep incisure on the greater curvature often indicates the presence of a posterior wall ulcer. In pyloric stenosis due to ulcer a large atonic stomach with a smooth outline at the point of obstruction is the rule, the ulcer crater being less frequently seen than in hour-glass constriction. Where perforation is suspected the barium meal is contraindicated, but a "flat plate" of the abdomen (a safe procedure) will often show an accumulation of gas above the dome of the liver. After a gross hemorrhage, roentgen examination should be deferred for at least two weeks after cessation of the hemorrhage.

Where the defect or crater shows an irregular outline or where there is not a definite decrease in size of a gastric defect in a period of a few weeks, carcinomatous ulcer must be suspected and exploration resorted to in order to clinch the diagnosis.

Treatment

The treatment of peptic ulcer resolves itself into three distinct procedures: the local treatment of the ulcer by mechanical means, the removal of the cause and the care of the complications.

1. The *local treatment,* as in the case of an ulcer in any part of the body, consists in putting the ulcer area at rest and in keeping it soothed so as to permit of healing. The stomach is never entirely at rest, but it is most active, even to the state of tetanic contractions, when empty. The normal hunger contractions are exaggerated in the presence of an ulcer and can best be relieved and prevented by keeping the stomach full of soothing food. The food should be sufficiently nutritious to permit of the body carrying on the healing process effectively, and where the patient is undernourished, should add to his weight. It should, like any diet, contain the proper balance of essential ingredients, and have an adequate vitamin content. While we do not feel that acidity plays any particular part in the production or persistence of an ulcer, combination with free acid and avoidance of over-stimulation of gastric juice are desirable. Daily bowel evacuation, while not essential, is encouraged by the frequent feedings, the drinking of sufficient water, the addition of yeast to the diet and the administration of mineral oil. General bodily rest is to be encouraged, although rest in bed is very rarely necessary. A suitable diet would be as follows:

Breakfast: Milk, 8 ounces, with cream if desired
Cereal, 5 ounces, with milk or cream
Egg, 1 soft boiled or poached
Bread or toast with butter
Fruit juice (at end of meal)

Midmorning: Milk, 8 ounces (cream ½ ounce, lactose, ½ ounce, or cocoa may be added if desirable)
Always with crackers, toast, bread or cake

Luncheon: Milk 8 ounces
Baked or mashed potato or plain spaghetti
Egg, 1 soft boiled or poached, or cream cheese
Bread and butter
Pudding, custard, gelatin or ice cream

Midafternoon: Same as midmorning.
Supper: Same as breakfast or luncheon.
At bedtime and during night (every 2½ hours, if awake): Same as at midmorning.
Olive oil, ½ ounce three times a day before meals.
Liquid petrolatum, ½ ounce at bedtime
Water, 6 or 8 glasses per day.

2. *The removal of the cause,* as discussed under the head of etiology, consists in the systematic and thorough eradication of all infective foci. Half-hearted removal of an abscessed tooth or infected tonsils is rarely sufficient. It is necessary to search for and remove all devitalized or impacted teeth, and root fragments, fillings or cysts remaining after extractions. Moderate pyorrhea may be kept under control by means of frequent scalings, but the ultimate cure of definite pyorrhea is extraction of the diseased teeth. Infected tonsils or tonsil remnants must be extirpated, and nasal, pharyngeal, sinus and ear infections must be eliminated. Such common sites of focal infection as the male and female genital tracts, the rectum and all other parts of the body must be expertly examined and thoroughly cleaned up. Failure to remove all infective foci, even though diet is strictly adhered to, will eventually result in recurrence of ulcer, although an exacerbation is undoubtedly hastened by dietetic indiscretions or nervous or physical strain. With the appearance of a new ulcer, complete check-up for neglected, recurrent or new foci must at once be instituted, and in our experience such foci are always found.

3. *The treatment of the complications* of ulcer includes the treatment of perforation, stenosis and hemorrhage. *Perforation* requires operation as soon as the patient has rallied from his shock (usually within the first two or three hours) the additional shock of too early operation often being the cause of unnecessary mortality. Operation during the first six to twelve hours results in the lowest risk. If not operated upon after twenty-four hours most patients die. Closure of the perforation by suture and covering with omentum is usually the best procedure, additional operative interference, on account of the increased risk involved, being carried out only where an obstruction is present.

Stenosis, whether due to hour-glass constriction or to pyloric or post-pyloric ulcer, also requires operation, but where the patient is depleted and dehydrated from prolonged vomiting a few days or even a week of preparation is worth while, reducing mortality and shortening convalescence. Such preparation would consist of frequent, small, liquid, concentrated feedings, subcutaneous and intravenous administration of chlorides and glucose and transfusions. Early feedings after operation and a proper dietetic régime afterwards, insure a good result. In the present article a discussion of the operative procedures is not desirable, but suffice it to say that the more simple the operation, the better it will be for the patient.

Gross hemorrhage is accompanied by shock and dehydration and is followed by a more or less severe anemia. Its treatment, which I have discussed in detail in a previous communication* involves the following principles:

*The treatment of gastric hemorrhage, Jr. Am. Med. Assoc., 1927, lxxxix, 1397-1400.

1. The promotion of blood clotting in the bleeding vessel; 2. The preservation of the clot when formed; 3. Treatment of shock; 4. Keeping the patient in the best possible general condition; and 5, Determining the nature of the lesion from which the hemorrhage originated. The first indication is absolute rest in bed, enforced by definite doses of morphine. This treatment combats shock and helps to check bleeding. Even though blood coagulation tests show normal findings, it is often best to use some form of medication to promote coagulation—horse serum, fresh or dried, thromboplastin preparations or whole human blood. A sudden increase in blood volume or blood pressure might tend to dislodge an early and unorganized thrombus, so that intravenous, subcutaneous or rectal fluids, and stimulants tending to raise blood pressure, should be avoided. In the presence of air hunger, transfusion of blood should be resorted to, but a small amount (250 cc. or less) will usually be sufficient. After ten days, one or more larger transfusions will materially shorten the period of convalescence. Feedings are instituted at once in order to prevent the sometimes violent hunger contractions, which so often are the cause of recurrent hemorrhage. The food should be soothing, should promote coagulation of blood at the bleeding point, should combine readily with gastric juice (to prevent digestion of the thrombus) and should not over-stimulate gastric secretion. Such a substance is gelatin, which is used in solution and to which later are added gruel and milk mixtures, cereals, puddings, soft eggs, etc., until a regular ulcer diet is reached at the eighth or ninth day after treatment. Complete gastrointestinal study is not begun until nearly two weeks after the hemorrhage. Ice should be avoided, internally because it produces hyperemia of the gastric wall, externally because it adds to shock.

Summary

1. So-called peptic ulcers are produced by the breaking down of areas of focal necrosis in the stomach wall, at varying depths below the mucosa.

2. They are the result of focal infection, the mechanism of their production being probably not direct infection, but some allergic or electrochemical reaction in the tissues involved.

3. They tend to heal spontaneously, each attack of ulcer symptoms being due to the development of a new ulcer.

4. The symptoms of ulcer are due to exaggerated hunger contractions and to retrostalsis.

5. The diagnosis of ulcer depends on history, roentgen ray and fractional gastric analysis.

6. The treatment of uncomplicated ulcer consists of diet and the thorough eradication of all focal infections.

7. Operative treatment is reserved for the complications of ulcer.

Malignant Melanoma with Delayed Metastatic Growths*

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MALIGNANT melanoma, frequently termed melanosarcoma or melano-epithelioma, is one of the most malignant tumors encountered in man. In some instances, however, the body seems to possess unusual resistance to metastasis from these tumors and it may be years after the appearance or removal of the primary growth before sudden, rapid and overwhelming metastasis occurs. This type of growth should, therefore, lend itself well to the study of the mechanisms of metastasis of tumors and bodily resistance to tumor growth, were it possible, with present knowledge, to approach such a study. The established observations of the delay in metastasis of these tumors are exceedingly important, not only in the diagnosis of this rare disease, but also because the prognosis may not be completely favorable in any case regardless of the time elapsed after excision of the primary growth. The present study has been undertaken with the view of presenting the histories of selected cases to reëmphasize these facts, and to record observations on the life history of the disease. There are few conditions apparently so readily cured in certain cases by simple excision as is melano-epithelioma, only to recur many years later in a rapidly fatal form following an interval of perfect health.

Malignant melanomas have been found to arise in several different organs of the body. The most common site is the pigmented mole of the skin and following this, in order, the pigmented areas of the eye, the anus and the suprarenal glands; such tumors have been reported as arising in the meninges, rectum, ovary, gastro-intestinal tract, gallbladder and other organs. There is considerable dispute as to the cellular origin of this type of tumor. It was formerly believed to arise chiefly from mesoblastic tissue and this, with the spindle type of cell which is commonly observed, led to the term melanosarcoma, which is still used. Certain observers believe it arises from the melanin-bearing chromatophores which are so widely distributed in the animal kingdom, although more recent interpretations place its origin among the epithelial cell group. Although the latter is the most commonly accepted view Ewing has recently accepted the work of Masson which would indicate that these

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tumors have their origin in nevus cells derived from and belonging to the end organs of peripheral sensory nerves. The cell form varies from spindle to round and, although most of these tumors are pigmented with melanin, occasionally nonpigmented melanoma is encountered.

The spread of these tumors may occur in three ways: by direct extension, by lymphatic vessels, and by the blood stream. Death within a month of onset has been recorded, but the usual duration of life, according to Coley and Hoguet, is two to three years. However, in certain cases in which there is definite resistance to metastasis, recurrence may not appear for as long as ten to thirty years after removal of the primary growth. The various modes of extension and the various types of metastatic growths will be illustrated by the case histories presented. Cases have been selected in which metastasis occurred after a period of at least five years after excision of the primary growth.

In each of the following three cases the primary growth occurred in a pigmented nevus of the skin and led to metastasis which did not become prominent until years later. At the time of examination these cases did not present the widespread metastasis which is the terminal stage of the disease.

Case 1. A woman, aged 43 years, registered at The Mayo Clinic in May, 1919, because of a tumor of the right thigh. Ten years prior to registration, a mole on the right thigh was accidentally irritated, following which it bled and later enlarged. Excision of the nevus was carried out at that time and the patient remained well until 1918, a year previous to coming to the clinic, when a brown area developed in the scar and gradually increased in size. Six months later she noticed swollen nodes in the right groin. Shortly thereafter anorexia and weakness began.

In the region of the scar there was a pinkish flattened area 4 by 2.5 cm., and in the inguinal region were many enlarged lymph nodes. Biopsy of these nodes showed melano-epithelioma. The patient died after she returned home.

Case 2. A woman, aged 48 years, came to the clinic in May, 1928, because of weakness of four years' duration. For fifteen years she had had a raised pigmented nevus on the left leg. Shortly after the appearance of the nevus it was cauterized, without recurrence, but six years later a tumor developed in the left groin, which remained unchanged for several years. Four years prior to registration the patient had severe menstrual hemorrhage at the time of the menopause and following this the tumor in the left groin continued to increase in size.

General examination was essentially negative save for a fixed, firm tumor, 3 by 5 cm., on the anteromesial surface of the left thigh. The patient refused biopsy and returned home. A diagnosis was made of metastatic melano-epithelioma of the left groin. The further course is unknown.

Case 3. A woman, aged 61 years, registered at the clinic in April, 1917, because of a growth in the left temporal region, which had started as a small lump one year previously. It grew rapidly and was cauterized a month later, but the ulcer which developed on the lump failed to heal and increased in size. Tincture of iodine had been applied locally on several occasions. The growth had been enlarging rapidly and was rather painful.

On careful questioning the patient recalled that twelve or thirteen years previously she had had a brown mole burned off the cheek just below the site of the present growth, which was a raised, rather firm growth 5 cm. in diameter, covered with blood crusts on the upper portion of the left cheek. Just below it was a similar area 2.5 cm. in diameter. There were no palpable cervical nodes surrounding it. The pigmented

area was excised. The pathologic diagnosis was melano-epithelioma.

The patient returned in September, 1917, at which time there was a small ulcer 1.5 cm. in diameter on the face, but no clinical or microscopic evidence of recurrence. She returned again in November, 1917, stating that her health had been good until six days previously, when she noted drooling of saliva from the left side of the mouth. Left hemiplegia and aphasia with some frontal headache and delirium, and then coma, rapidly developed. Death occurred two days later.

At necropsy there was a large healed scarred area on the left upper malar region with atrophy and scarring of the skin. There were several areas of metastatic growth in the lungs, and bronchopneumonia. Excessive hemorrhage had occurred in the left internal capsule of the brain, and into all the ventricles, with thrombosis of the left lateral sinus. Although it could not be definitely determined, there was some suspicion that a metastatic melano-epitheliomatous growth was present.

It should be pointed out that following excision of the primary growth local recurrence may or may not take place, and that if local recurrence is present it may occur immediately following excision and remain stationary for years, or it may not be present until years later at the time of widespread metastasis.

The four cases of the second group are illustrative of the presence of distant metastasis in the absence of local recurrence in the skin

Case 4. A woman, aged 42 years, came to the clinic in June, 1926, because of a lump in the right groin, of four months' duration. In 1920 she first noted rapid growth of a pigmented mole on the calf of the right leg. The following year, the mole, which had become 2.5 cm. in diameter, was excised (elsewhere) and a diagnosis of sarcoma made. Because of this, the popliteal area was dissected out a few days later. She had no further trouble until February, 1926, when pain developed and a lump was noted in the right groin. There was some question as to whether the lump had grown during the succeeding months.

General examination disclosed a large irregular fixed mass in the right groin which seemed to extend into the right side of the pelvis, where a large firm mass could be palpated. The scars of the previous operation appeared normal. A diagnosis was made of metastatic melano-epithelioma, and the patient returned home following treatment by irradiation. The outcome is unknown.

Case 5. A woman, aged 53 years, came to the clinic in March, 1927, because of frontal headaches of two months' duration. The pains radiated to the occipital region, and they were persistent and intense. Nausea and vomiting, and vomiting unaccompanied by nausea, occurred. The patient was drowsy and lethargic, with diminished vision and drooping of the left side of the face. Ten years previously a mole had been removed from the left side of the face; it had recurred several times and was removed each time. Two months preceding registration a small black tumor behind the left ear had been observed.

General examination disclosed moderate obesity, lethargy, nystagmus and paralysis of the left side of the face. There was a firm tumor, 1.5 by 1 cm., below the left ear. It was somewhat tender, and movable. Ophthalmologic studies revealed bilateral choked disks of 4 to 5 diopters each, with hemorrhages and exudates in the retina. The roentgenogram of the thorax was negative. Biopsy of the tumor below the left ear disclosed melano-epithelioma, and a diagnosis was made of brain tumor (metastatic) and melano-epithelioma in the left temporal region. The patient returned home. Further data as to the outcome are not available.

Case 5 presents several interesting points. First, it illustrates the persistence of the growth in spite of continued cauterization and yet the long delay before the resistance of the patient was lowered or the virulence of

the tumor raised to the point of metastasis. Second, it illustrates the advantage of biopsy of a suspicious cervical or cranial node in the presence of an obvious intracranial neoplasm, for it not only clinched the diagnosis in this case, but it saved the patient a needless exploratory operation as well. Third, it is an instance of the rare case in which the presenting symptom of the metastatic growth is that of an intracranial lesion, and it is probably the type of case in which intracranial metastasis will be fatal before widespread metastasis is evident.

Case 6. A man, aged 35 years, first came to the clinic in May, 1929, because of migraine and chronic nervous exhaustion. He returned in March, 1930, because of numerous subcutaneous lumps which had appeared in October, 1929. There had been slight swelling of the right testis for a few months preceding this. About twelve firm, painless subcutaneous nodules were scattered over the torso, all of which had progressively increased in size. The patient had grown increasingly pale, lost 10 pounds in weight and had a dry hacking cough. Malignant melanoma was reported following biopsy of one of the tumors (elsewhere). There was a history also of removal of a nevus from the right calf in 1923 or 1924.

On general examination fatigue was apparent. Numerous subcutaneous dark nodules, 0.5 to 2 cm. in diameter, were noted. On the inner side of the right calf there was a clean scar where the mole had been excised. The abdominal examination was negative, as was the roentgenogram of the thorax. A diagnosis was made of malignant melanoma with metastasis. The patient returned home, where he died three months later of generalized metastasis.

Among the interesting features of this case is the absence of evident local or regional recurrence of the melanoma excised six years previously. This is unusual, considering the fact that the lesion originated in the skin, which practically always gives evidence of local recurrence or of metastasis to the regional lymph nodes. The only clinical evidence of metastasis in this instance was the subcutaneous nodes, and it should be mentioned that this patient had been subjected to careful examination ten months previously, at which time the nodes were absent.

Case 7. A man, aged 33 years, first came to the clinic in 1920, at which time a pigmented nevus on the skin of the left deltoid area was excised. There had been some recent increase in the size of the nevus prior to its removal. Thereafter the patient continued in his usual good health save for occasional attacks of vague abdominal pains, the exact nature of which could not be determined. In June, 1930, he returned to the clinic complaining of pains of two months' duration in the lower part of the abdomen. The pains occurred several hours after meals, and were associated with backache, fatigue, and loss of 15 pounds in weight.

General examination was essentially negative, but laboratory tests revealed secondary anemia (10.2 gm. hemoglobin for each 100 c.c.), and occult blood in the stools. Roentgenographic examination of the stomach disclosed a small polyp. At abdominal exploration multiple malignant polyps were found scattered throughout the small intestine, one of which had produced intussusception of the lower part of the ileum. The patient was unable to withstand the operation and at necropsy widespread metastasis of malignant melanoma was observed. Six cauliflower-like pedunculated and sessile growths were found in the right auricle of the heart, the largest 2.5 cm. and the smallest 0.7 cm. in diameter. In the lungs were numerous firm nodules 2 mm. to 2 cm. in diameter. Similar metastatic nodules were observed in the liver and spleen (one nodule). The stomach was dilated and presented a polyp on the posterior wall 7 cm. from the pylorus. There were many small masses scattered throughout the duodenum, jejunum, and ileum, the largest of which measured 5 by

3 by 1.5 cm. They occurred as sessile, pedunculated or ulcerating areas, greater in number high in the small bowel. The colon and rectum were free of metastasis. Microscopic study revealed pigmented epithelial tumor cells with both adenomatous and epitheliomatous formation, and the diagnosis was made of malignant melanomatosis with multiple metastasis.

The remarkable features of this case were the misleading symptoms which the patient presented. The gastro-intestinal symptoms were outstanding and there was no suggestion of malignant disease until the time of operation when the carcinomatous polyps were discovered. It was the presence of intussusception which led to surgical interference. A similar case of metastatic malignant melanoma and intussusception of the small intestine has been reported by Maxwell. The presence of widespread metastasis to the heart, lungs, liver, spleen and stomach and small bowel revealed the hopelessness of the condition and yet it had been ten years since the excision of the primary growth.

The last group, which comprises three cases in which the eye was the site of the primary melanomatous growth, is perhaps the most interesting and clinically the most startling of the series.

Case 8. A man, aged 43 years, came to the clinic in June, 1930, because of weakness and an abdominal mass of six months' duration. Seven months previously he had had a heavy cold with slight fever and thereafter he continued to have bouts of mild fever, malaise, pains in the joints and weakness. Four months previously he first noted a painless, somewhat movable mass in the right upper abdominal quadrant which later enlarged and moved toward the median line. Because of a sense of fullness the appetite failed, although there was no indigestion or jaundice. Further questioning brought out the fact that in 1916, fourteen years prior to registration, the left eye had been removed because of "acute glaucoma following detachment of the retina" and in 1929 he noted the appearance of dark colored nodules on the right wall of the thorax anteriorly, at the base of the neck, in the left axilla, the groin, and near the spine. These areas were painless, movable, and had not changed in size during the last year.

The patient was slightly emaciated and numerous firm movable black nodules were noted. The abdomen presented a hard nodular mass with a definite border coming down to the umbilicus in the right upper quadrant, and the spleen was palpable. A roentgenogram of the thorax disclosed an area of increased density in the right lower lobe, probably metastatic. Tests of hepatic function disclosed dye retention graded 4, indicating marked hepatic disease. Biopsy of one of the inguinal nodes was reported as melano-epithelioma. The diagnosis was made of melano-epithelioma involving the liver and abdominal lymph nodes. The patient returned home, where he died two months later.

Case 9. A man, aged 55 years, came to the clinic May 12, 1930, because of pain in the right upper quadrant of the abdomen and loss of weight. He had been in his usual good health until six or eight months before admission, at which time illness which was called influenza by his physicians developed, with increasing weakness and gas on the stomach. Although the respiratory infection rapidly cleared up, the feeling of abdominal distention became more pronounced and soon moderately severe continuous pain developed, starting in the epigastrium and passing to the umbilicus. Two months before admission he had first noted the appearance of painless, subcutaneous lumps over the sternum and left shoulder. About this same time the gastro-intestinal symptoms improved, but six weeks before admission a pressing pain developed beneath the right costal margin which bothered him, especially at night. He had lost 20 pounds in weight. In general he felt well, with the exception of some weakness and slight cough with mucoid expectoration. In 1920, his right eye had been enucleated because of a tumor.

Biopsy of one of the subcutaneous nodules removed elsewhere had been diagnosed sarcoma.

The patient was slightly emaciated. The orbit from which the right eye had been enucleated did not give evidence of recurrence of growth. There were numerous, scattered, firm, freely movable, painless, subcutaneous nodules over the scalp and thorax. The axillary and cervical lymph nodes were large and there was a large firm irregular mass, presumably the liver, in the right upper quadrant of the abdomen. A few râles were noted at the bases of the lungs. Laboratory studies showed mild secondary anemia with 12.6 gm. of hemoglobin for each 100 c.c., and the roentgenogram of the thorax disclosed multiple metastatic granules. A diagnosis of multiple metastatic tumors throughout the body was made, the source undoubtedly being the tumor of the eye enucleated ten years previously.

Case 10. A man, aged 53 years, came to the clinic November 18, 1930, because of stomach trouble which he had had for twenty years. The distress was a typical ulcer type of dyspepsia which became pronounced two months before admission. During this time he had suffered from constant epigastric pain which radiated to the right upper and lower abdominal quadrants and up into both sides of the thorax. Relief from food or alkalies was incomplete. There were no other gastro-intestinal symptoms and he had not lost weight. In 1920 the right eye had been enucleated on account of sarcoma of the eyeball.

The patient was emaciated. The tissues of the right orbit appeared normal. A small firm, freely movable, subcutaneous nodule had been present over the third thoracic vertebra for a year. A large, firm, irregular, scarcely movable and tender mass was palpated in the right upper abdominal quadrant; presumably it was the liver. Laboratory examination disclosed slight secondary anemia; the hemoglobin was 13.5 gm. Roentgenograms of the stomach disclosed an extrinsic mass. A diagnosis of melanoma of the liver was made.

The points of similarity of these three cases are quite remarkable. The patients had all undergone enucleation of the eyeball for tumor (in the first case "detachment of the retina for glaucoma") ten or more years previously, apparently with success and with good health through the intervening period. In each case the presenting complaint was of epigastric pain focusing the attention on the abdomen, and on examination the liver was found to be large, firm, and irregular, obviously the seat of malignant disease. Each patient also presented one or more subcutaneous nodules, although there was no evidence of local recurrence within the orbit or of regional metastasis. The essential data of these cases are compiled in the tabulation (page 210).

Comment

Malignant melanomas arising within the pigmented nevus comprise the majority of such tumors. The various modes of metastasis have been illustrated in the case reports. There may be local recurrence of the growth following excision, metastatic involvement of the regional lymph nodes, or of neighboring organs, or widespread metastasis throughout the body.

The varying clinical picture observed in the localization of metastasis may be explained in four different ways: (1) it may depend on the occurrence of metastasis by way of the lymphatics, in which case transportation of cells by superficial lymphatics would lead to metastasis in the regional nodes, while transportation by deep lymphatics may lead to metastasis in more distant lymph nodes or even widespread dissemination through the thoracic duct and blood stream; (2) the metastasis may be by the hemato-

genous route, in which case widespread metastasis is more probable; (3) the clinical picture may depend on the stage, early or late, in which the disease is observed, and (4) the quality and quantity of metastasizing tumor cells may be the determining factors, as pointed out by Armstrong and Oertel, since with a small number of cells the localization depends on qualitative selection of suitable organs for extension of metastasis, while with large quantities of cells this qualitative restriction is overcome and widespread overwhelming metastasis occurs. At present, there is no method of predicting which means of dissemination will be followed by a melanotic tumor in a given case.

There is just as much variability in the time elapsing between the occurrence of malignant changes in the nevus and the development of disseminated metastasis as there is in the selectivity of routes of dissemination. The occurrence of these two factors is so well established that they need no further defense.

In each case cited there was growth of the pigmented nevus just prior to excision or cauterization. Such a change therefore immediately justifies a guarded prognosis as to the occurrence of metastasis following removal of a growing nevus. The impression should not be obtained that dissemination is bound to occur once visible proliferation of the original nevus has begun, but the point to be emphasized is that one can never be absolutely certain, even after many years, that widespread metastasis will not occur. It would seem that the treatment of choice in such cases would be not only wide excision of the offending nevus but of the regional lymph nodes and intervening lymphatic vessels as well, as emphasized by Handley. The occurrence of bleeding, ulceration or crusting of a pigmented nevus should always be taken as a serious warning and be followed by immediate excision, as already mentioned.

Malignant melanomas arising within the eye comprise about one third of the whole group of malignant melanomas and are generally regarded as taking origin in the choroid, ciliary process, iris and conjunctiva. The more recent work, however, seems to indicate that they arise in the pigmented layer of the retina. This confusion is the result chiefly of failure to observe early cases histologically. The mode of extension from the eye, according to Dawson, may be in three directions: (1) by direct extension; (2) by lymphatics to the cranium, or more rarely to the cervical nodes, and (3) by the blood stream, chiefly to the liver. Among the numerable cases in the literature in which metastasis has been delayed for many years following excision of the primary growth are those of Wilder, thirty-two years; Schilling, twenty years; Lawbaugh, seventeen years; Fisher and Box, fourteen years, and Hutchinson, Lilley, and Dobbertin, ten years. The syndrome is so well established that when one is confronted by a patient with a glass eye and a large abdomen or liver the suspicion should immediately be aroused that a malignant melanoma has metastasized, regardless of the number of years since enucleation of the globe. Malignant tumors within the eye are nearly always primary for, as Cordes and Horner have pointed out, metastatic tumors to the eye are

rare (seventy cases of metastatic carcinoma to the eye are reported in the literature, chiefly from the breast), and there are only four recorded cases of metastatic melanoma of the skin with metastasis to the eye. Such metastasis usually occurs in the uveal tract. Metastasis from one eye to the other seldom occurs; consequently a malignant melanoma of the eye can be regarded quite safely as primary in that organ. Such statements as those of Karsner that "the pigmented choroid tumor is extremely malignant and secondary foci or metastasis develops very early" cannot be accepted for all cases, as has been illustrated.

Malignant melanomas arising in other organs have not been cited in the present study because delay in metastasis from such tumors has not been observed, chiefly because the primary tumor is not viewed as readily as are those in the eye or skin. Although melanomas conceivably may arise wherever melanin-bearing cells occur, their occurrence primarily in the stomach or small intestine is questionable. The usual involvement of the liver and occasionally of the gastro-intestinal tract in the absence of a known primary growth has led to the belief that the primary tumor may be in these organs, particularly if the patient's history is unknown. The secondary tumor in the small intestine may have all the appearances of a primary growth, as occurred in one of the foregoing cases, and also in the case cited by Saphir. Saphir's experience led him to conclude: "Reports of primary melanotic tumors of the intestine should be regarded with suspicion."

Delay of metastasis is probably more accurately called delayed metastatic growth, for it is logical that the metastasis, or at least the dissemination of tumor cells, must take place before or during the successful operative removal of the primary growth. The mechanism of this phenomenon of delayed growth is not certain.

It is not difficult to understand the entrance into, and transportation of tumor cells by either the blood stream or lymph stream in the development of metastasis. Similar phenomena probably occur in the development of metastatic abscesses, foci of infection, or orchitis in mumps, and possibly also the so-called calcium metastasis in which this inorganic salt is carried from the bones to the lungs, stomach and kidneys. The development and growth of metastatic cells is so commonly observed that little attention is paid to the mechanisms by which they occur. It is this part of the development of metastasis which is so little understood. In this consideration Oertel stated: "It must be appreciated that transportation of tumor cells and even arrest of tumor plugs are not identical with metastasis, for the conception of metastasis requires further a participation of the local tissues in the growth of cells to a tumor by furnishing the tumor cells with a vascularized stroma. . . . The local susceptibility determines more than transportation of tumor cells the development of the metastasis."

The delay of metastasis must depend, therefore, not on any altered transportation of the tumor cells but on their delay in growth, and that this delay in growth may be for many years is a remarkable phenomenon. The actual transportation and distribution of the tumor cells must be very wide-

spread since the liver is so frequently involved secondarily. This would necessitate the passage of the cells through at least one or more capillary beds, probably two, that is, the pulmonary and portal.

The inhibition of growth of the transported tumor cells in certain organs over many years is evidence, perhaps, of failure of adequate powers of resistance of the organ or of the presence of an aggressive "formative irritant" (Oertel) in the tumor cells in their relation to the affected organ. Cohnheim stated: "Only when and where tissues are lowered in their physiological metabolism by age, atrophy and inflammation will metastasis be possible." This would indicate that the resistance of the organ must be lowered before actual metastatic growth occurs and this may in fact be due, as Symmers put it, to some alteration in the "equilibrium of function in the cell (tumor) itself" or possibly to the occurrence of trauma. When such a point is reached the organ is stimulated to the development of a "vascularized stroma" and the growth of the cell deposit occurs with fulfillment of the conception of metastasis. Such hypothetic considerations will be replaced in time by more accurate facts as our knowledge increases, but for the present we are uncertain what influences suddenly fan the coals to flames when the metastatic growths appear.

It should not be supposed that malignant melanomas comprise the only group of tumors in which delay of metastasis occurs. Other types of tumor may show the same phenomenon and because of this the "three-year or five-year cures" of malignant tumors can not always be accepted. This is particularly well illustrated by such a case as that reported by Stacy and Vanzant in which an apparently inoperable carcinoma of the uterine cervix treated by radium seemed to heal and yet seven years later at necropsy metastasis in neighboring lymph nodes showed evidence of apparently recent, active carcinomatous growth.

There are several other points of clinical interest. The primary growth in malignant melanoma, unless it is within the eye or the brain, is not usually of great clinical significance. It is the widespread dissemination which usually destroys life, and death does not occur until widespread metastasis has occurred. This property applies to few other known tumors. McWhorter and Cloud found that in the nine cases of malignant melanoma which came to necropsy at the Bellevue Hospital widespread metastasis was present in each case and the liver was usually affected. Metastasis to the liver is present in the end stage in almost every case of this disease. This is an interesting phenomenon which cannot be explained at the present time except by the lowered resistance of the liver. Lymph nodes are not necessarily involved in every case.

The subcutaneous nodules observed as metastases may readily be misinterpreted as sebaceous cysts, as actually happened in one of the cases reported here.

From the medicolegal standpoint the delay of metastasis of these tumors may be very important, for the removal of the primary growth may occur in a period either covered or not covered by clauses in insurance policies or other legal papers, whereas the metastatic growth may occur years la-

SUMMARY OF CASES

Case	Age, years, sex	Primary Growth		Site of Metastasis	Appearance of Metastasis, years	Diagnosis	Chief Complaint	Outcome
		Site	Treatment					
1	43F	Mole on anterior surface of thigh	Excision	In scar and inguinal nodes	8.5	Biopsy of nodes	Tumor of thigh for six months	Died; time?
2	42F	Mole on calf of right leg	Excision	Inguinal nodes and pelvis	5	Biopsy of original tumor	Lump in right groin for four months	Unknown
3	48F	Mole on left thigh	Cautery	Anterior surface of left thigh	6	Clinical history and examination	Weakness for four years	Unknown
4	61F	Skin of cheek	Cauterization	Local recurrence and lungs and intracranial sinuses	12	Postmortem examination	Lump on face for one year	Died seven months after excision
5	53F	Mole on left side of face	Removed; several recurrences	Brain and behind left ear	10	Biopsy of mass on left ear	Headaches for two months	Unknown
6	35M	Mole on right calf	Excision	Subcutaneously; right tonsil	6	Biopsy of subcutaneous nodes	Subcutaneous nodes for five months	Died nine months after secondary metastasis
7	33M	Nevus on left arm	Excision	Heart; spleen; stomach; intestines; mesentery; lymph nodes; liver and lungs	10	Postmortem examination	Weakness and lower abdominal pain for two months	Died after operation
8	43M	Eye	Enucleation	Liver and subcutaneously	13	Biopsy of inguinal node	Weakness and mass in abdomen for six months	Died two months later
9	53M	Eye	Enucleation	Liver and subcutaneously	10	Microscopic examination of original tumor	Indigestion; abdominal pain for six months	Unknown
10	55M	Eye	Enucleation	Liver; lungs; bones; and subcutaneously	10	Biopsy elsewhere; sarcoma	Subcutaneous and abdominal tumors for two months	Unknown

ter under different legal conditions. The knowledge of delayed metastasis of malignant melanomas may be of prime importance under such circumstances.

The treatment of malignant melanomas is unsatisfactory; they show practically no response to any type of irradiation therapy.

SUMMARY

Ten cases of malignant melanoma arising in the skin and the eye with removal of the primary growth followed by delayed metastasis over periods of five to thirteen years are recorded.

These tumors recur and metastasize in various ways: by local recurrence, by metastasis to the regional or distant lymph nodes, by widespread metastasis throughout the body, especially to the liver, or by a combination of these. It is the dissemination of metastases and not the primary growth which leads to death.

A conception is presented of the mechanism of delay in growth of the metastatic areas.

Studies of these cases reveal the value of the long-time study of a given disease in an individual case so as to become familiar with the complete life cycle of the disease.

BIBLIOGRAPHY

1. ARMSTRONG: Quoted by Pepper.
2. COHNHEIM: Quoted by Pepper.
3. COLEY, W. B., and HOUGUET, J. P.: Melanotic cancer: with a report of 91 cases, Ann. Surg., 1916, lxiv, 206-241.
4. CORDES, F. C., and HORNER, W. D.: Metastatic melanoma of both eyes: report of case, Jr. Am. Med. Assoc., 1930, xcv, 655-658.
5. DAWSON, J. W.: The melanomata, their morphology and histogenesis; a study of cell origins and transformations with a critical discussion on aspects of tumor growth and a clinical review, Edinburgh Med. Jr., 1925, xxxii, 501-732.
6. DOBBERTIN: Melanosarkom des Kleinhirns und Rückenmarks, Beitr. z. path. Anat. u. z. allg. Path., 1900, xxviii, 52-56.
7. EWING, JAMES: The problems of melanoma, Brit. Med. Jr., 1930, ii, 852-856.
8. FISHER, HERBERT, and BOX, C. R.: Pigmented tumour of the eyeball: death from multiple pigmented carcinoma nearly fourteen years after excision of the eye, Brit. Med. Jr., 1900, i, 639-640.
9. HANDLEY, W. S.: The pathology of melanotic growths in relation to their operative treatment, Lancet, 1907, i, 927-933; 996-1003.
10. HUTCHINSON, JONATHAN, Jr.: Quoted by Schroeder.
11. LAUROBAUGH: Quoted by Schroeder.
12. LILLEY, C. H.: Quoted by Schroeder.
13. MASSON: Quoted by Ewing.
14. MAXWELL, W.: Secondary melanomata of small intestine with chronic intestinal obstruction and intussusception, Med. Jr. Australia, 1928, ii, 656-657.
15. MCWHORTER, J. E., and CLOUD, A. W.: Malignant tumors and their metastases, Ann. Surg., 1930, xcii, 434-443.
16. OERTEL, HORST: Outlines of pathology in its historical, philosophical, and scientific foundations, 1927, Ed. 1, Montreal, Renouf Publishing Co., 479 pp.
17. OERTEL, HORST: Quoted by Pepper.
18. PEPPER, O. H. P.: Metastasis, Internat. Clin., 1924, ii, 269-286.
19. SAPHIR, OTTO: Metastatic melanoma of the jejunum: report of a case, Arch. Path. and Lab. Med., 1927, iv, 22-25.
20. SCHROEDER, M. J.: Late metastasis of melanosarcoma of the liver, Med. Jr. and Rec., 1924, cxix, 601-603.
21. STACY, LEDA J., and VANZANT, FRANCES R.: Poisoning from cinchophen. Minnesota Med., 1930, xiii, 327-328.
22. SYMMERS: Quoted by Pepper.
23. WILDER, W. H.: Quoted by Schroeder.

The Hospital
Its Relation to the Community and to the Medical Profession*

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IN the aggregate, the operation of the hospitals of the United States falls in the class of Big Business. With less than one thousand hospitals fifty years ago, we now have 7,000 hospitals in the United States. The value** of the hospital plants is about three billion dollars. The annual cost of maintenance is about 900 million dollars. The amount spent for new construction each year is 200 million dollars. The hospitals provide over 900,000 beds, in which every day there are over 700,000 patients. There are over 650,000 persons*** employed in operating hospitals, not including doctors and nurses. These hospitals treat about 12,000,000 patients each year. Further elaboration is unnecessary before this audience. I ask you to keep this picture in mind, however, with reference to topics which I shall discuss later.

Time would not permit a full discussion of all phases of the subject assigned to me. Therefore, I shall confine myself to a discussion of some mooted questions. That there are such questions you well know. One has only to think of the numerous articles, by both medical and lay writers which have appeared in magazines and daily papers during the past few years, to be convinced, not only that there are questions requiring answers, but that there exist both general interest in and general lack of accurate information concerning most points under discussion. These articles deal with the cost of hospital service, doctors' fees, nurses' fees, the amount of free work done both by hospitals and doctors; in fact, they constitute a general discussion of the cost of medical care.

Doctors criticise (a) the cost of hospital service, particularly to private patients; (b) the cost of nursing service; (c) the amount of out-patient service; (d) the creation of diagnostic clinics; (e) the lack of accommodations for people of moderate means, and (f) the closed staff organization.

The question of costs will be discussed later. With reference to Out-Patient Service, there is no doubt that this phase of work has been much extended in recent years. There are now 5,000 dispensaries for poor people. These have been established to meet a

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**Rorem—"The Public's Investment in Hospitals."

***Allon Peebles—Publications of the Committee on the Cost of Medical Care.

real need in the communities served and have, in most instances, been sanctioned, if not recommended, by the staff members or medical boards of the hospitals. Rarely have such enterprises been undertaken by trustees or hospital managers independently of the staff. Can any one doubt the need of such services? Not if one were familiar with the types, and the large number, of patients flocking to the dispensaries.

Much has been said about dispensary abuse by patients. Repeated investigations have shown that such abuse is at a minimum, rarely, if ever, over two per cent. This would seem very low, probably no greater than the abuse of doctors' private offices. On the other hand, the hospital is criticised, if its officers attempt to check carefully the claims of the patient for free treatment or treatment at a low fee and if patients are admitted free. The same criticism applies to the admission of in-patients. In other words, the hospital is damned both ways. I believe it not only right, but desirable, that patients should be made to pay something, if possible. To make it too easy to obtain free treatment would be bad from every point of view, both for the patient and the doctor. Furthermore, comparatively few persons will choose a dispensary service except for the sole reason that they cannot afford to pay for the service elsewhere.

Patients are often admitted to dispensaries who pay a fee equal to that charged in some private offices. This is criticised. This does not occur often enough to offer any real competition and in most instances, this initial fee is seldom repeated, although the patient returns repeatedly for further treatment. It would be unsound practice to send such a patient away only to return later for continued treatment. There are many faults in our system, but they are not confined alone to the hospital or dispensary.

Recently articles have appeared berating the system which depends upon the gratuitous service of physicians. One writer suggested that physicians might organize and refuse to serve on the staff of any hospital or dispensary unless paid. I am sure that such a suggestion would be condemned promptly by the profession as unwarrantable and foolish, certainly it would be condemned by all who gave serious consideration to our system of hospitalization and its support. Of this I shall speak later. It is undoubtedly asking a great deal of busy doctors to give their service to the operation of dispensaries. On the other hand, many physicians have found it instructive and helpful in building up their experience which, particularly to the young man and the internist, is his greatest asset. The same is true to an even greater degree of the service rendered in the care of patients in the public wards of hospitals. Under the present system, the man who obtains a staff appointment, which calls for some of his time in caring for ward patients, receives quite as much as he gives; except, perhaps, those who have long since become well established and no longer need the hospital service for the experience and the prestige which such a connection undoubtedly gives. It is obvious that until a more stable basis of hospital support is found, hospitals will not be able to pay physicians

for services to the poor in the public wards and dispensaries.

The development of diagnostic clinics for people of moderate means is not at present a great menace to medical practitioners, but it may be a factor of considerable importance in the future, unless the medical profession finds some other way of satisfying public demand. Undoubtedly, in the present era of specialization, people of moderate means feel that they simply cannot face the bill, resulting from being referred from one specialist to another, and some other system must be devised. Perhaps more well trained general practitioners will be the answer, perhaps group practice, as advocated by many, will be the answer. But if the latter, it must be on a basis of an inclusive fee, not separate fees of individual men merely grouped together for convenience and for cutting down overhead. In any event, the medical profession should find the solution; not the hospital, not the state, not the public health administrator; although, possibly, all should cooperate. However, some, or all, of these agencies will attempt the solution independently unless doctors attend to the safeguarding of their own field.

That hospitals have, in the past, paid too little attention to the provision of accommodations for people of moderate means is undoubtedly true. Such is likely to happen in the rapid expansion of any system, particularly if as haphazard as that of hospital development in this country. We concentrated first on the care of the poor; next came the provision of accommodations for the well to do. The reasons are obvious.

It was necessary to provide for the poor because in no other way could they obtain proper care. The development of more complicated methods of diagnosis and treatment, and particularly the developments of surgery, made it desirable to provide at least the same opportunities of service for those who could pay as for those who could not. Furthermore, it has been the theory that by carrying a goodly number of private patients who could pay well for their accommodations, the overhead would be so distributed as to make it possible to render service to a larger number of poor persons. In more recent years it must be admitted that, in many hospital developments, perhaps undue attention has been given to the private patient class, particularly where those developments have been financed by general public subscription. Here it must be admitted that perhaps doctors have a right to criticise, because it has not infrequently happened that the public probably provided the funds under some misconception. It has been universal practice in campaigns for funds to emphasize the service to be rendered to the community, implying, at least, service to the poor and unfortunate. In reality, such movements have often resulted in the building of hospitals from funds raised by popular subscription which were very largely for private patients and for the benefit of a comparatively small group of doctors. Those doctors on the outside have had ground for criticism. Had the campaign literature or pronouncements stated frankly that so many beds would be provided; that most of them, the exact number being stated, would be for private patients;

that only staff members would have the privileges, their names being given, no criticism would have been justified. But such campaigns have seldom been run on such straightforward and businesslike lines.

In recent years more attention has been paid to the people of moderate means. Hospitals are now attempting to provide this class with suitable accommodations at rates within their means. That this service has been lagging is not alone the fault of hospital trustees and administrators. We are all at fault. But some questions remain to be answered. Can such accommodations be provided at rates which will make the service self-supporting or must such a service be endowed? No definite answer which can apply generally has yet been found. Such a service can be made self-supporting in some localities, but, in determining where and how, we must consider the type of service to be rendered, the community to be served, the type of building required, the restrictions of the building code, and so on.

In large urban centers, where fire proof construction is demanded and where the most complex type of medical and surgical service is demanded, this question has not yet been answered satisfactorily. Boards of trustees are often faced with the situation that funds at their disposal have been given for charitable purposes and may not be used for this purpose. Therefore, unless self-supporting, endowment funds must be obtained. If a building is required, that means additional funds for that purpose. The Massachusetts General Hospital in Boston has embarked in this field in a manner which should shed much light on the subject. It is important to know that the authorities of this institution decided, after careful consideration, that a building accommodating 300 patients represented the right sized unit which would offer a chance of operation on a self-supporting basis. An initial gift of $1,000,000 was supplemented by other funds, bringing the total to about $2,000,000 for the building. One of the large foundations promised $150,000 to help offset any deficit for the first three years of operation. The prices range from $4.50 per day for a bed in a nine bed ward to $6.50 per day in single rooms. There are extras for operating room, x-ray, laboratory fee, etc. This unit, known as the Baker Memorial, has been open not quite a year and it is too early to know exactly how this experiment will work. It is significant that the authorities have stated publicly that such an undertaking could not succeed without the cooperation of the medical staff, the members of which agreed in advance to limit their fees to the patients in this building.

The closed staff is also criticised by doctors. The limited, or so-called closed, staff is generally favored for several reasons. It is believed by many that a carefully selected staff, members being chosen because of demonstrated ability and a capacity to work in harmony with others, will result in a more workable unit, with the maximum of standardization in all procedures, and will result in better care of patients and more economical operation. I believe this has been demonstrated to be true. There can be no argument on the point that all doctors are not of

equal ability. Not all members of a closed staff are of equal ability, but if the principle is sound and its application is made solely on the ground of ability, then that staff should be composed of men competent for the work assigned to them, supplementing each other and forming the best type of a working organization.

The Trustees must be satisfied that members of the Staff are competent and responsible, because in many states charitable hospitals are not liable for damages provided the governing boards have exercised due care in the selection of their officers and employees. It is also a fact that if poor work is done or glaring mistakes are made by a doctor in treating a patient in a hospital, the reputation of the institution suffers quite as much as that of the doctor concerned.

The point has been made that all public or community hospitals should be open to any reputable physician or surgeon in that community, arguing that only in this way will the general level of practice be kept on a high plane. That is yet to be demonstrated. On the other hand, I believe that if such a system were followed, those hospitals would not be as efficient in operation, nor as productive in developing outstanding men, nor in clinical and laboratory investigation, as under the restricted staff type of organization. Human nature is such that no matter what organization is adopted, even if all doctors were accorded hospital privileges, a considerable number, because of personal characteristics, insufficient background, or general incapacity, would always remain in the rut of mediocrity. In any event, the welfare of the patient is the first consideration.

We must admit that the public at large has a definite interest, often a vested interest, in the welfare of hospitals. Yet the public is not well informed and, in consequence, is unduly critical. It is perhaps our fault that the public is not better informed. Some of the misinformation or lack of information is due to the manner in which appeals for funds are made, a point which I have already touched upon. Then, the public's advisors, as represented by the medical profession, are not always well informed because they are too busy to give careful thought to the subject and sometimes these same advisors are too ready to agree with the public. It is always open season for hospitals. It seems to me a very short sighted policy on the part of physicians, to criticise, as so often happens, without any constructive effort, those institutions which mean so much to the profession by way of the opportunities provided for their convenience and which are absolutely essential for much of their work. These men with hospital privileges have provided for them, and without cost to them, more facilities than are provided for any other professional group.

The public is critical of the cost of operation, resulting in numerous appeals for funds and high charges to patients, and because patients are sometimes turned away. The last point is often played up by newspapers. It should be obvious that a hospital, like any other building, has limited capacity, and even an urgent case must at times be referred elsewhere.

Furthermore, why should a hospital be expected to do more than its finances permit? In this period of unemployment, hospitals have been hit hard because of the increased number of patients unable to pay. For the most part, they have assumed the extra burden without assurance of additional funds. It is expected that hospitals will do this humane work. Are hotels expected to feed the hungry, do railroads and street cars transport the poor and unemployed free of charge, and do stores supply the necessities of life to these people without cost? Certainly not; no one expects it. But hospitals are expected to assume the burden on the theory that the public supports them. All would be fine if this were true.

Hospitals are expensive institutions to operate, much more so than twenty years ago. Why? For the same reason that the cost of living is much higher. The character of hospital service is much more thorough, more efficient, and more complex than formerly. The quarters provided have been made increasingly more elaborate, more comfortable, and are provided with equipment for efficient service far beyond the provisions of earlier years. Any medical man familiar with hospitals will concede these points without debate.

To be more specific, all articles of food and supplies of all kinds, cost much more. The old system of hard, soft, and liquid diets is no longer sufficient. We must have well organized dietetic departments which will provide diets of many kinds and varieties; cardiac, nephritic, diabetic, high calorie, low calorie, salt free, high protein, low protein, and so on. This involves not only a constantly greater variety of articles to be prepared, some unduly expensive, but also infinitely more labor in preparation and service.

The service is much more complex, as exemplified in the greater care with which patients are studied, the more numerous tests employed, such as x-ray, fluoroscopic, basal metabolism, blood chemistry, bacteriological, serological, physiological, and biological. Treatment is also more complicated. More nursing service is required, larger resident staffs are needed, and likewise, more employees of all types. The modern hospital now requires a working personnel of about two persons for every patient and sometimes more. The planning of a hospital now provides smaller units for patients, the large open ward belongs to the past. This is necessary for the proper segregation of patients and their greater comfort. Hospitals cannot, and should not, rely entirely upon student nurses for nursing service as was the case in the past, with daily duty covering 12 or 14 hours. Shortening the working day for nurses, providing maids to do many of the household duties formerly assigned to the pupil, and the employment of more graduates, has increased the cost of operation enormously. The extensive developments of out-patient service, of social service, of follow up, of efficient record departments, provision for hydrotherapy, electrotherapy, light therapy, radium therapy, mechanotherapy, are all factors which have entered into the increased cost of hospital operation. They have all resulted from the demands of the profession because of increased knowl-

edge of disease and its treatment. No one should find fault with that.

In discussing the attitude of the public towards the numerous appeals for funds we must all have some sympathy. We must go back to the basis upon which our hospital movement was conceived in order to explain the situation. In these days of super-efficiency, every enterprise not yielding a profit is under question. The vast majority of our hospitals are small, providing less than 125 beds each. They are financially handicapped to begin with, and must do considerable free work. Where can such hospitals obtain competent, well trained business managers. They are not available for such small institutions. These hospitals, therefore, for the most part, must rely upon nurses as managers. Have they been taught business management? No more than the doctors. A more conscientious group of workers it would be hard to find, most of them are overworked, are trying to do effective work for which they have never been trained, and are worried and harassed all the time. Sometime there will be a place where they can be trained specifically for such a job and then, perhaps, the job will be better done and they will command larger salaries and worry less. But I am sure that no more sincere and conscientious effort will go into their work. Until that time comes, however, these hospitals and their communities will have to be content and would do well to appreciate what they have.

Governing boards should know what the job demands, should know what qualifications the persons possess whom they select. If they are unable to obtain those who are thoroughly competent, they should help those whom they do select, not condemn them. Of course, changes are often needed, but those instittutions which change managers every year or two frequently have something wrong with them other than the superintendent.

The larger hospitals, able to pay for competent service, are, I believe, for the most part, well managed. You cannot compare a hospital with an industrial plant with its well paid skilled labor and closely knit organization, all operating to the end that a standardized product shall be turned out as economically as possible, all costs being absorbed and a percentage added for profit. Hospitals are not engaged in that type of business. The hospital industry is engaged in mending broken bodies, in removing diseased tissue, in taking a machine which is out of order and causing it to function smoothly once more, and to continue functioning. No two problems are quite the same because no two individuals are quite the same, either physically or mentally. Furthermore, while we can and do carry business methods into every phase of hospital operation, there is a point where standardized procedure and business methods stop. That is where the doctor begins to function, in the professional care of patients. The doctor is successful because of his own individuality, his own method of doing the job, and his own personality. He is individualistic in his methods and it would be a sad day when the attempt was made to standardize him, if it were successful.

I referred to the basis upon which our hospital movement is founded. Has the growth of the hospital movement resulted from a carefully studied plan based upon the needs of the population? Have the 7,000 hospitals been established according to a definite program of so many beds per 1,000 population, so many beds for this branch of medicine, so many for that, based upon the needs of the communities to be served? You know that such is not the case. Is the movement the result of well established policies of the state for serving its citizens, such as the principle underlying our public school system? It has been a haphazard development depending for the most part upon the medical profession and groups of interested laymen and is based largely upon the principle that it is the duty and privilege of people of means to provide for their less fortunate neighbors. It is a beautiful principle and it has worked remarkably well, but is it sufficient to meet the requirements of the future?

The time has come when haphazard methods should be replaced by logical, sound methods based upon facts and sound principles.

To be more explicit, we have our Boards of Education which determine the number and type of schools needed, we have Chambers of Commerce, and Commissions for Industrial Development to look after the commercial interests of cities. Is it not equally important that we have some machinery to consider the hospital requirements? To be sure, we have our State and City Charity Departments and Health Departments, but considering the handicaps under which such departments operate, we would none of us wish to place our hospitals under those agencies. I make the point that the time has come when there should be machinery of the State or the municipality which should concern itself with such questions as "Is another hospital needed, where, of what type, and how is it to be supported?" I do not mean that it shall run the hospitals. But such a commission should determine the needs of the community and should pass upon all new projects before they are undertaken and so long as our hospitals must depend largely upon public support, should determine how much of the expense should be borne by the State or its political subdivisions and how much by private philanthropy.

Of all the hospitals in the United States:*

49 per cent are of the private or corporate type,
26 per cent are federal, state, or municipal in type,
25 per cent are private or commercial in type.

We know that, generally speaking, the states and counties concern themselves principally with hospitals for the tuberculous and the insane. The cities provide some general hospital beds but not nearly enough. There are 5,600 community hospitals of which 4,300 are general hospitals. Generally speaking, excepting for the insane, the tuberculous and veterans in Federal Hospitals, the care of the sick poor rests largely with the corporate or community hospitals. Is this statement well founded? A recent survey** of the hospitals in Philadelphia

*Publications of the Committee on The Cost of Medical Care.

**By Nathan Sinai, D.P.H., and Alden A. Mills, Committee on Cost of Medical Care.

disclosed that 40 per cent of all patients in all hospitals were free. In New York City, the 30 general hospitals participating in the proceeds of the United Hospital Fund provided, during the year 1929, 2,532,000 days of treatment, 44.2 per cent of which were free. These are certainly fairly typical of the situation in the east and perhaps to a lesser degree, in the west; where more general hospital beds are owned, and operated by the state and its subdivisions.

Who pays for this free work? The Survey in Philadelphia disclosed these figures for the 52 hospitals. Of the gross income available for operating these hospitals (excluding the Philadelphia General—a city institution)

58.7 per cent came from patients
16.5 per cent come from endowments
4.8 per cent came from cash contributions
9.5 per cent come from Federations
7.4 per cent come from public support—city

In other words, these hospitals did 40 per cent free work and received from public funds 7.4 per cent of their total revenue and had a total deficit aggregating $355,779.00.

I fancy this is quite typical of most cities varying, perhaps, slightly up or down. And yet, in most states, if not all, real estate owned by these private hospitals for purposes of revenue and even the endowment funds, the income of which is used for the poor, are taxed by both state and city and at the same rates as any other real estate or securities which may be owned and used for the profits of business or of individuals.

It is worth while to analyze the above figures somewhat further. About 43 per cent of the money available for operating these hospitals comes from sources other than payments of patients, and of this 43 per cent, only 7.4 per cent comes from public funds so that about 35 per cent comes from endowments, cash contributions, or the federations, which means, that in one way or another, this amount comes from private philanthropy.

It is significant that at this time, with the long history of the development of American hospitals back of us, the total endowment fund of hospitals is estimated to be $437,000,000;* of which $15,000,000 is for governmental, $3,000,000 for proprietary, and $419,000,000 for the community or non-profit hospitals. This amount of endowment for the non-profit hospitals is sufficient to fully endow 13,967 beds, of which there are 247,970 in this group of hospitals. The endowment is only sufficient, therefore, for 5.6 per cent of the beds. It is further significant, that of the 2,604 hospitals operating on the non-profit basis, only 1,060 control any endowments, and of this number, 125 hospitals control 45 per cent of the total, and only 31 of these control more than $2,000,000 each. Many hospitals in the United States do not receive endowment income in sufficient quantities to materially affect their financial policies. The point of all this is that the system is not sound, that with the increased cost of hospital operation, it is doubtful if the present

*Figures supplied by Rorem in his book entitled "The Public's Investment in Hospitals."

system of support will prove adequate for the future.

We certainly must not discourage private philanthropy, but would the system not be on a better basis if the burden were more equitably distributed by requiring the cities and states and counties to pay more nearly what it costs these hospitals for caring for the poor? It is stated that dependent persons are ill, on the average, nearly twice as often as persons with incomes considered adequate. The U. S. Children's Bureau,* in a study of 22,967 births, between the years 1911 and 1916, in eight cities, found that in families, where the earnings of the father were above $1,250, there were 59 deaths per 1,000; that the number of deaths of infants increased per 1,000 the lower the earnings of the father: for example, earnings $850 to $1,050, deaths 82.2; earnings $650 to $850, 107.5 deaths. Warner in American Charities gives illness as a cause of dependency in from 20.1 per cent to 43.7 per cent of dependent families. Considering these facts, would it not seem to be quite as important that we provide adequately from public funds for the care of the sick and for public health generally, as for education, for good roads, bridges, and harbors, all at public expense? Certain it is that until this or some other method is found, the public must expect appeals either separately or through community chests.

The public also protests against high charges in hospitals. In the 30 general hospitals in New York City, referred to above, the average daily per capita cost was $6.79. Generally speaking, we may say that the average per capita for general hospitals is probably at least $6.00 per day. If the cost of public wards was distinctly separated, still the cost would be considerably more than the average charge in the public ward, which is generally about $3 per day, rarely more than $3.50. That does not seem high. To be sure there are extras, but for ward patients these are usually reduced to a minimum or remitted.

Private room rates are much higher, ranging in the more expensive types of service, from $7.50 to $15.00 per day, depending on size, location, with or without bath, etc. The average per capita cost for private room service is without doubt higher than the lower priced rooms, probably about the same as the average price charged for rooms. As a business proposition, this is not excessive, when one considers that the public will cheerfully pay the same price at a hotel and get much less for the money. In the hospital one receives, in addition to his room, three meals a day, some nursing care, services of the resident staff, orderlies, and maids, ordinary medication, surgical dressings, etc. To be sure, the extras are heavy in most hospitals. I think the principle of charging extras on a cost basis would be sound if credits were likewise offered where standard service is not used, but this would entail a complicated system of accounts and even hotels do not do that. Generally speaking, I believe it would be better to eliminate all extras, if practicable. Many hospitals have gone part of the way in this, but I do not think we can go all the way, in

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fairness to the average patient, who would thus be obliged to pay for the fads and fancies of the rich or cranky individual whose demands either directly, or indirectly through his physician, are often excessive. In determining the question of costs per day for private patients, it must be remembered that in most instances the buildings are given to the hospital and it is rare that hospitals include in operating costs any interest charge on capital invested or any allowance to be set aside to care for depreciation and obsolescence.

There is considerable criticism of the charges made by graduate nurses and of the need of employing graduate nurses in hospitals. I believe the charges of graduate nurses are not too high. They work long hours and must deal with situations which are most exacting, and sometimes, most unpleasant. They have periods of unemployment, sometimes long periods. The private duty nurse earns, on the average, between $1,200 and $1,300 per year, and her years of active service are limited. She is indispensable and her lot is hard, although satisfying from the standpoint of service. By comparison with other lines of employment open to educated women, her earnings are too small rather than excessive.

As to the complaint against the need of employing special nurses in hospitals, a survey was made by a national committee covering 1,892 private patients who had specials and this showed that in 40 per cent of the cases the doctor urged a special on account of special care needed, in 33 per cent the family wanted a special, in 22 per cent the patient felt the regular service inadequate, in 3 per cent the hospital suggested one, and in 2 per cent the reason was that their friends always had one. I believe, however, that hospitals should provide more adequate nursing service, but they cannot do it under the present system.

The average duration of stay in the hospital, particularly for most surgical patients, is about half as long as was the case 25 years ago. This means that even if the hospital charge is double, the total hospital bill for that type of patient would be no greater than it was 25 years ago.

Considering all of these factors, I believe the charges are not out of line, although they seem high when the hospital bill, doctor's bill and special nursing fees are totaled. I believe the complaints rarely come from the man who can afford it, but generally from those less fortunate in this world's goods, which probably brings us again to the needs of those of moderate means.

Then, too, we must take into consideration that the average man has made no provision for illness. He resents illness anyway, and doubly resents the attendant expense. He has not denied himself in other respects, however. Wingate Johnson, in an article in the March "Atlantic Monthly" furnished these figures on the expenditures of the average family. He compares the cost of medical care with other items of the average family expenses per year:

For doctors	$24
For medicine, chiefly patent	25
For hospitals	15

For nurses	8
For pleasure automobiles	150
For tobacco	67
For candy	37
For gasoline	37
For theaters	35
For soft drinks, ice cream, etc.	34

In the study of the cost of medical care in Philadelphia, conducted by Nathan Sinai and Alden B. Mills of the staff of The Committee on The Cost of Medical Care, the total bill for medical care is given as follows:

Total cost			$104,000,000
For physicians, dentists, nurses, and cults			47,000,000
Physicians	$27,000,000	Principal items of the above figure	
For dentists	13,000,000		
For osteopaths, chirop., midwives, etc.	3,000,000		
For patent medicines	obtained in drug stores		9,000,000
For prescriptions			7,340,000
For home remedies			3,692,000
For miscellaneous medical care sales			2,380,000
For hospitals, sanitoria, etc.			16,000,000
For indirect costs not included in operating costs of hospitals			7,206,000

Some other minor items are not given here.

The point is that the total cost of operating all of the hospitals is not the largest item by any means. The public spent for medical care sales in drug stores, a total of $22,986,000, of which over $13,000,000 was for patent medicines and home remedies.

But it is of little use to criticise the public because it spends so much for home remedies and patent medicine. While it is true that if there was less high pressure salesmanship and people spent less for radios, automobiles, electric refrigerators, electric washing machines, movies, etc., they would have more money with which to meet doctors' bills and hospital bills, finding fault will not remedy the evils of the situation. We shall doubtless face these same problems for a long time to come, but it is well to know the facts.

Many remedies have been suggested, and among the most prominent have been:

The formation of guilds for the purchase of medical and hospital service,

Health insurance, compulsory or voluntary,

State medicine.

I am sure you have definite ideas on these subjects. The guild idea may be a good one; it sounds attractive; but in our present state of social development, and particularly in the larger cities, I doubt if it would appeal to the class which presents the great hospital problem, the free and part pay patients. The same applies to insurance, unless compulsory, and therein lie dangers of many varieties.

In the very multiplicity of agencies and individuals concerned in the provision of medical care lies perhaps an outstanding weakness in our present system. It may well be that from the medical standpoint, the greatest need is not for more hospital beds, not for more doctors, or more public health activities, but is an agency for the organization and co-ordination of all medical facilities so that each may render its greatest usefulness to the public and may co-operate most effectively with all others in best serving the interests of those concerned in purchasing and paying for medical care.

The Profession and the Public*

By George Edward Follansbee,** M.D., *Cleveland, Ohio*

THERE are two points of view from which to look at medical economics, that of the profession and that of the public. The standpoint of the members of the medical profession has been consistently occupying the pages of state and other medical journals for years. The complaints and arguments of the doctors have been reiterated until you are familar with them. The public has had its hearing in many popular magazines and weeklies and in the newspapers. The public never sees the medical journals presenting the complaints of the profession and few of the profession read any large proportion of the complaints of the public in the magazines. Neither side has a proper appreciation of the other.

I wish to bring to your attention some thoughts aroused by some of the more moderate criticisms by the public against our profession. In doing so I wish to be understood plainly as making no malicious charge against an honorable profession to which I am proud to belong. The spirit is rather one of analysis and constructive criticism based upon the opinions formed about us by those who are not of us—an attempt to see ourselves as others see us, a wise thing to do at times.

The great cry is that it costs too much to be sick or to raise a family. I am not interested tonight in any cost except that of the doctor which approximates only about 25 per cent of the entire cost of health, sickness and reproduction. The impression has gained a strong hold on the better educated and more prosperous of the people that a general practitioner is not qualified to practice medicine: he might do as a distributor to direct to the proper specialist, or as a nurse, but that he is incompetent to actually take the responsibility of the care of illness, accident, childbirth or that latest entity, a healthy baby. So specialists are called and visited, clinics where routine methods multiply costs are sought in many trivial complaints, the costs rise and the medical profession is berated for excessive charges and accused of rank commercialism. It is unfortunately true that the profession is contaminated by some members who apparently took their oath to Mammon rather than to Hippocrates, but their number is small in comparison with that great body of men who always have and always will follow the

*Read at the Baltimore Meeting of the American College of Physicians, March 24, 1931.

**Chairman Judicial Council, American Medical Association; Member Executive Committee, The Committee on the Costs of Medical Care.

ideals of the Hippocratic oath. We apologize to the public because of them. We do not defend them.

The number of self-styled specialists is ridiculous. It should be unlawful for a doctor to present himself as a specialist unless he has had adequate training and taken a degree in his specialty. That is something the medical profession of itself cannot accomplish but it can assist toward that end. Medical schools can revise their curricula as one step, teaching less of the intricacies of the specialties and more of the general course of preventive and curative practice which comprises seventy-five per cent of the family's needs, all of which can be cared for by a properly educated general practitioner. Much could be done toward this end by the thousands of open hospitals refusing their facilities to men for the care of cases which they are unqualified to treat. This is being successfully done today in some open hospitals with striking and convincing improvement in the mortality and morbidity rate, and lower costs to the people for hospital and funeral expenses. Also, the occasional specialist who gets much of his work from similarly unmoral colleagues is likely to overcharge for his services and be unprofessionally insistent upon collection. The temptation to pay commissions is likely to be beyond his power of resistance.

The statement that there are too many specialists applies to cities, especially the large ones, where most of the complaint of the high cost of medical care is made. It does not apply to towns and rural districts. Failing the correction of the rapid diminution in the number of general practitioners, of the excessive trend toward specialism, of the lawfulness of any or every doctor announcing himself to the people as a specialist, of the present almost prohibitive cost of some essential diagnostic procedures, of the commercializing of our profession by a small minority of its members, the excuse is valid for government and philanthropy and business to take over sections of practice, large or small, which should remain in the domain of private practice. The whole profession and particularly the real specialists should support the general practitioner and encourage the public to make all proper use of him. A specialist should return to the care of the referring physician all cases sent to him as soon as the need for special ability or special treatment is past. He should refuse to treat those cases coming to him over the head of a family physician when that physician could and would care for the case satisfactorily. It should be beneath the dignity of a specialist to care for such cases.

The older general practitioner is suffering from an inferiority complex. He is depressed and saying little, though he might say much, for he has seen the exceedingly rapid scientific advance of the practice of medicine with which he has been unable to keep pace. He realizes his limitations, but he does not realize that his years of experience have taught him an art of practice which will offset in many cases his lack of scientific knowledge, and of which his young competitor is ignorant.

The graduate of the last few years is quite competent to care for much

of the work that now goes directly to specialists and people should be taught so. We must re-establish the confidence in the general practitioner, the family physician; we must confine the work of the specialties to that requiring peculiar knowledge, ability or apparatus; we must practice medicine for the benefit of the people with financial gain honestly secondary in our thoughts, or inevitably the people with the assistance of private or public philanthropy will provide what we refuse to supply, medical care at a cost they are able to pay.

A very large proportion of whatever cost is excessive is due, not to the profession, but to the people themselves. This appears in the many instances in which people seek the services of the well known and most prominent specialists whose only way of restricting their work to their physical capacity is to charge fees commensurate with their reputation. It is evident in the demands by the people themselves for services of which they have heard but which in the particular case are not necessary for diagnosis or treatment. It is shown in the tendency of the public to look upon physiological pregnancy, child-birth and the rearing of children as a pathological process requiring the service of the specialist in all cases instead of only those with pathological complications. It is manifest in the habit of ignoring the general practitioner and primarily consulting some specialist who in the opinion of the patient is the proper one to treat the condition, only to find that the trouble is a local manifestation of a condition not within his proper sphere of activity. To the extent that people themselves seek the services of a specialist for conditions which can be satisfactorily cared for by the general practitioner, they themselves are responsible for the excessive cost. Twenty to twenty-five per cent of them do not choose the right specialist in the beginning and so costs are pyramided.

These are matters for which we are only remotely responsible but which we should try to correct by education of the public, by advice and remonstrance to our patients, by recognition of the utility and ability of the general practitioner and by upholding the dignity and standing of the specialties by confining their work to conditions requiring expert ability and knowledge. We have a more direct responsibility in respect to those practices which are under the direct control of the members of the profession themselves.

Fault is found justly or unjustly with the practice of medicine in too many ways to consider all of them. The principle complaints are, (a) excessive charges for operations, (b) prohibitive expense of children, (c) unwarranted cost of diagnosis.

Operative Costs

Excessive charges for operations refer of course only to the surgical specialties and complaint is made most directly and most frequently against general surgery.

There was a time not many years ago, when a specialist was a specialist by virtue of his superior ability and because the general practitioner expected to care for all the illnesses and accidents occurring in his clientele ex-

cept those of major severity. These he referred to a specialist if one was available. Graduates of those days were impressed with the dignity and exclusiveness of expert special work and had deep respect for the responsibility involved in major procedures.

As medical education and technique advanced, ideals as well as the training of the student changed. Specialties were divided on a basis of anatomic fields instead of personal ability. The idea grew that any condition occurring in an anatomic field belonged to that anatomic specialty. The change to this conception magnified the available field of the specialty to the student, minimized his comprehension of the knowledge and ability required and blunted his conscientious appreciation of his responsibility, until now the intention and expectation of the majority of graduating interns is to enter at once on the practice of a specialty in its entirety, usually general surgery, following general practice only so far as needed as a stepping stone to full specialization.

Many surgical procedures which formerly were considered major, by virtue of advancement in knowledge, technique and hospital routine are now essentially minor. The present graduate who has served his time as intern and resident is competent to perform many operations which formerly justly belonged to the surgical specialist. Should these men restrict their ambition to operate to those cases in which they are competent; should the surgical specialist admit the competency of these men in this limited field; should the public be educated to accept them for such operations; should these men themselves recognize that the operations which they are competent to perform are essentially minor and regulate their fees accordingly, much of the cry about the excessive charges for operations would be stilled. By recognition of this principle many would be satisfied to be general practitioners who now aspire to be specialists, and the hospital mortality and morbidity rate would be reduced. A recent survey of the physicians of two of our large cities shows that on the statements of the individual physicians themselves, twenty-eight per cent are complete specialists, thirty-seven per cent are partial specialists and only thirty-five per cent are general practitioners. The people cannot support a medical army with so many generals. There must be more privates. The effect of present medical education and professional aspiration has been to increase the field of the specialty and along with it the number of specialists, and as a necessary corollary has restricted the field for, and the number of, general practitioners. The opposite should occur.

The tendency of partial specialists to over-value their services has already been noticed. The code of ethics for years has declared that too low charges are unprofessional, on the basis of harm to the public. Too high charges are harmful though for a different reason and are equally unprofessional. This matter therefore is to a degree under the control of medical organization. In so far as this abuse exists and comes to the attention of medical organization, in self-preservation and devotion to professional ideals cogni-

zance should be taken, for the reputation of the whole profession is sullied by the reprehensible acts of comparatively few.

Children Costs

The popular cry that the production of a family of children is too expensive now-a-days invites one to ponder the cause of such a condition. Some years ago the birth and raising of children was taken as a matter of course quite like the buying or building of a home. The greatest concern until the child entered school was the furnishing of food and clothing. It was all normal like other health. The confinement which turned out badly was looked upon as a "sickness" just as was any other departure from health. Today, how different! The human being from germinal cell to school age, in the popular attitude, is a pathological entity and the process of its being seems to be accepted as pathological throughout its course, except at its beginning. During the last ten years the act essential to impregnation has been transferred from the moral and spiritual field of contemplation and is now generally allocated to the purely physiological. On the contrary pregnancy, child-birth, infancy and childhood have been transferred from the physiological to the pathological field. Quite naturally, the result has been to increase cost. Greenhouse tomatoes cost more to produce than field-grown ones.

My intention is not to deride all prenatal work, obstetric specialists, well-baby care and pediatrics. They all have their legitimate place but they are all over-emphasized; there has grown up a mild national hysteria on reproduction which is involving the major portion of the populace wherever the various specialists can be found. Who started it and who keeps it alive, whether political public health or voluntary charitable agencies, the medical profession or the people themselves, will be answered according to the point of view of the individual answering. But whoever is responsible, the system has been over promoted. It is costing too much and we should return—not to the former status but to a common sense basis. What is there so profound or abtruse about prenatal work or raising normal babies that a general practitioner is incapable of giving satisfactory service? What expertness is needed in a normal confinement that requires a high priced specialist to be within call while an intern and obstetric nurse watch the progress of labor so as to call the obstetrician at the proper time to be present at the delivery?

The general practitioner is sufficiently well trained to do all a specialist does in a normal confinement, or should be if he is not. The field of the obstetrician and the pediatrist should be in the abnormal or unusual case, called in by the general practitioner when his skill is insufficient. Babies and children do cost too much under the present system but the system should be changed. Our part in the change individually and collectively, is to educate the people to "render unto Caesar the things that are Caesar's" and to teach the general practitioner to "render unto God those that are God's." Pressure should also be brought on medical colleges, if needed,

to educate the student sufficiently well in obstetrics and pediatrics to give all needed care to normal cases and be able to recognize those conditions which need knowledge and ability beyond his own. The public will be benefited. The general practitioner will be elevated to his proper dignity in the profession. The specialist will lose none of the work which properly should be his.

I have chosen to speak particularly of those specialties about which complaint is made most loudly by the layman. Critical examination of others would develop some justifiable cause and lead to corrective suggestion. Internal medicine while not yet subdivided to the same extent as surgery, is tending that way, much, I believe, to the detriment of both public and profession. And it has its weak spots.

Diagnosis Costs

I will conclude this critical, and I hope, constructive analysis by discussing the third feature calling down upon our heads the greatest amount of complaint, the unwarranted cost of diagnosis, a subject which involves us all. Diagnosis! The interesting case! It is the most attractive game in medical practice. It is to medicine as the mystery story is to literature. We all play it. We all are entranced with it. The autopsy or the operation proving our acumen is like the reading of the last pages of the story to test our accuracy of deduction. Without that last proof we are unsatisfied.

Tests in chemistry, bio-chemistry, physics and physiology have multiplied until we are bewildered by the signs, reactions, interpretations and indications. And many of these cost money. Someone must pay. If the patient can he must, though the cost of scientific laboratory diagnosis may overshadow the other expenses connected with his illness. If all these are needed to make a diagnosis or direct his treatment he should pay for them. But many such expensive procedures are carried out which are not essential to correct diagnosis. They are the luxuries of medical practice. The rich want them and should have them. The man of restricted means may want them but he should not have them. They are sometimes ordered for the doctor's own satisfaction or to teach interns. Such a use is proper in the case of the rich or the free patient but is unwarrantable in the case of the ordinary pay patient. When a doctor orders examinations for which the patient must pay he is at the time the guardian of the patient, the trustee of his funds. Such meticulous care and sound judgment should be exercised as would be expected of a similar legal relationship. It is the doctor's duty even to remonstrate when the patient in his ignorance suggests or requests needless expensive examinations. There is no relationship requiring such a high grade of honor to exist as that between the patient who places his life and his pocketbook without redress in the keeping of a doctor and the doctor who accepts that trust. It is to the everlasting honor of the medical profession that that trust is so infrequently abused. It is more frequently abused in thoughtless enthusiasm than in willful violation, but the results are the same to the patient.

There is some justified complaint of routinely passing the patient around from one specialist to another because certain anatomic fields may be involved. Needless to say the same conscientious consideration should be exercised as in the ordering of laboratory examinations.

The matters which have been brought to your attention are not amenable to change by organized medicine. The change in attitude by profession and public must come from the thoughtful sympathetic consideration, the conviction and the dictum of the scientific leaders of the profession, the members of the special societies. Through these influential men the public can be educated. Public opinion is the driving force which determines policies in this country. The medical profession is no less subject to it than is business or politics. With the help of the sensational, the propagandist and the welfare press a tide of public opinion inimical to the profession is rising which has already become a distinct menace. That the logical result of such opinion as is now being formed, will in the end be incalculably harmful to the people as a whole will make no difference for the mass of the people do not think logically. The medical men themselves must do the thinking and the educating of the public. The first step in this education is to correct within the profession all justifiable complaints against the practice of medicine that are possible of correction. And all are possible of correction if the scientific leaders realizing the danger have the will to correct. Then we can come to the people with clean hands. Then with sincerity and conviction we can educate the public. Organized medicine has the machinery and the power of defense against adverse opinion but it cannot form public opinion and cannot ultimately prevail against a rising tide. Resolutions and articles in medical journals do not reach the layman and would be discredited if they did. It is only by public and private pronouncement by the scientific leaders, upheld by the influential men of the profession that the change can come. It is to you men of the special scientific societies that the profession must look for leadership.

Editorials

CINCHOPHEN POISONING A PARTIAL EXPLANATION FOR THE INCREASING INCIDENCE OF ACUTE YELLOW ATROPHY

Acute yellow atrophy of the liver is by no means the rare condition now that it was when it occurred almost solely as a disease of pregnancy and of the puerperium. Since then it has been shown that the toxic necrosis produced by chloroform, particularly in the condition known as delayed chloroform poisoning, is indistinguishable in its pathological features from acute yellow atrophy. That syphilis alone may produce marked changes in the liver parenchyma came to be generally accepted and in combination with arsenical therapy, syphilis was found to give the full clinical picture of acute yellow atrophy. In susceptible individuals arsenical drugs alone and in usual therapeutic doses were proved to be sufficient. In the munitions factories during the war and in industrial uses since, such substances as trinitrotoluene, trichlorethane and carbon tetrachloride have been found capable of producing extensive hepatocellular necrosis of this same general type. The parenchymatous lesion of phosphorus poisoning is distinctive in its early stage by reason of the diffuse fatty degenerative infiltration which it produces, but in the reparative stage it may be confused with the hepatitis produced by the other agents mentioned. Some have claimed that alcohol found in combination with other substances in home-distilled and synthetic beverages, is the cause of the increase in acute parenchymatous degenerative hepatitis of this type. Moreover, most of these livers now are not seen in the acute stage by the pathologist, but only when reparative changes are well established, with extensive bile duct proliferation as an attempt at liver regeneration. These are examples of what may well be termed subacute 'acute yellow atrophy' and chronic 'acute yellow atrophy'—a true toxic cirrhosis in a reparative phase. There is full proof that the cinchophen (phenylquinolincarboxylic acid) group of drugs has had a share, how important can only be surmised, in increasing the incidence of acute yellow atrophy of the liver. Although 'atophan' was introduced in 1908, it was not until 1925 that the first report of a fatality from the use of this group of drugs appeared, but the occurrence of jaundice had been previously noted in numerous instances. Since 1926 the cases have multiplied rapidly. Within the last few months several excellent papers* have appeared giving evidence

*Parsons, L., and Harding, W. G., Cinchophen (atophan) poisoning, report of four cases, Am. Jr. Med. Sc., 1931, clxxxi, 115-125; Sherwood, K. K., and Sherwood, H. H., Acute toxic hepatitis (acute yellow atrophy) due to cinchophen, Arch. Int. Med., 1931, xlviii, 82-88; Beaver, D. C., and Robertson, H. E., The specific character of toxic cirrhosis as observed in cinchophen poisoning, Am. Jr. Path., 1931, vii, 237-257.

of the widespread interest in this condition. Beaver and Robertson have reported five fatal cases from the Mayo Clinic and have described in detail the various stages of the liver injury and its attempted repair. Sherwood and Sherwood collected forty-eight cases from the literature and added one. From these cases they have built up a composite clinical picture which is exactly like that of acute yellow atrophy as formerly known. In some instances symptoms have arisen as late as ten days after the cessation of administration of the drug. At first there is nausea and gastric irritability followed shortly by the onset of jaundice, biliuria and pruritis. The jaundice deepens and at this stage progressive decrease in the size of the liver can be demonstrated. By the third and fourth week, if the patient is not to recover, the jaundice and toxemia have increased and splenomegalia, ascites and edema of the extremities may develop. Finally the patient becomes delirious, and then comatose and dies. It appears that re-administration of the drug, even in small quantities, will usually produce a prompt return of jaundice. This indicates, then, that use of the cinchophen group is contraindicated in patients who give either by history or by clinical findings evidence of previous or present liver disease. Unfortunately, physicians are not always aware that various antirheumatic preparations, distributed under sundry trade names, belong to this group. Oxyl iodide, farastan, atophan, diiodatophan and biloptin are all cinchophen drugs and by all of these toxic parenchymatous hepatitis has been produced. A predisposition or idiosyncrasy, dependent upon as yet unknown factors, seems to be significant in determining that an acute yellow atrophy will result.

SUICIDES IN THE UNITED STATES IN 1930

According to the compilation by Frederick L. Hoffman which appeared in The Spectator of May 14, 1931, there were 6,440 deaths by suicide in 99 American cities in 1930. This yields a death rate from this cause of 20.0 per 100,000, the highest figure since 1915. On the basis of these statistics it is believed that the annual loss of life by suicide in the Continental United States must reach 18,000 to 20,000. The nation-wide industrial and business depression has undoubtedly played a large part in the increase in the total number of suicides for the past year. From the medical standpoint the changing trend in the means chosen for self-inflicted death is of considerable interest. There are fashions and modes in suicide as in all other human activities. We have passed through a period in which much newspaper publicity was given to poisoning by bichloride of mercury and to various means for combatting that condition. As a result, there was an increase in the homicides in which mercurial compounds were the active agent. The suicide record for 1930 shows that jumping from high buildings and other high places is becoming an increasingly frequent method of self-destruction. In many cases it has been found impossible to determine whether death by this means was an accident or a suicide. There were at

least two suicides recorded during the year of persons who jumped from airplanes while in flight. Extreme caution should be used in guarding high places in various ways, such as by protective devices, and in making it impossible to open the cockpit doors of airplanes except at the will of the operator or an attendant. The annually appearing statistical study of the suicide problem which Hoffman has prepared for so many years has done much to keep this question before the public eye. He properly insists that there is much that is remaining undone which would go far toward preventing this wastage of human life.

MORTALITY RATE FOR THE FIRST SIX MONTHS OF 1931

From various sources come reports that the first six months of the present year have been unusually healthy. Out of the tripartite combination of general business depression, closing hospitals and idle doctors, and general good health, has arisen the opportunity for the columnist and jokester to aim his thrusts at the medical man for it appears that it brings good health when people generally cannot afford medical attention. Others find the explanation in less extravagant living, plainer food and more hours of sleep. However, figures recently released by Dr. Henry F. Vaughan, Commissioner of Health, giving the mortality record for the City of Detroit for the first six months of 1931 show very clearly that the reduction in mortality has involved such widely diverse diseases that economic factors alone cannot provide an adequate explanation. As compared with the first six months of 1930, deaths from tuberculosis decreased 20 per cent and the pneumonia death rate fell from 116.5 per 100,000 to 92.2 per 100,000. The death rate from diphtheria declined to less than one-half its former level and deaths from meningococcus meningitis decreased 77 per cent. Only deaths from cancer showed a slight increase, rising to 72.3 per 100,000 from 70.3 per 100,000. The rate for heart disease remained the same at 147 per 100,000. All important causes of death except the two last mentioned showed significant decreases. If this condition continues Detroit will have the lowest death rate in 1931 that that city has ever had. It is evident that the lowered mortality occurred throughout a wide range of infectious, and therefore preventible, diseases. In part, at least, hospital wards are poorly filled because there are fewer people ill, and the most important reason why there are fewer people ill in 1931 is that medicine is intrinsically altruistic. For the period reported upon, the death rate for typhoid fever for Detroit was but .37 per 100,000, approximately one in 300,000. As compared with conditions of fifty and sixty years ago the saving for health and life from this one disease will explain not a few empty hospital beds.

Abstracts

Traumatic Miliary Tuberculosis. By JEAN FIRKET. (Rev. belge des Sci. méd., 1931, iii, 532-547.)

Two illustrative cases furnish the basis for a discussion of the pathogenesis and medicolegal significance of miliary tuberculosis following trauma. In one instance a young man died 21 days after receiving a severe blow upon the head. At autopsy an active tuberculous meningitis with scattered miliary tubercles in lungs, spleen and kidneys was found. An old caseating focus was found at the hilus of the right lung. In the other case there was chemical trauma to the respiratory tract by the inhalation of ammonia. Death occurred 12 days later. Young miliary tubercles and early exudative foci were found in the lungs, spleen, kidneys and meninges. There was an old hilus lesion. It was decided that these two cases could properly be considered examples of traumatic miliary tuberculosis. It is suggested that the following points must be established before admitting a causal relation between trauma and the development of a miliary tuberculosis:

1. The reality of the accident;
2. That the clinical symptoms and particularly the fever did not appear until some days after the trauma;
3. That there were no clinical evidences of the development of a tuberculosis before the traumatism;
4. That the diagnosis of miliary tuberculosis was confirmed at autopsy, and the distribution of the lesions found to conform with the clinical signs, and
5. That an older latent or recently activated lesion of tuberculosis was also established by autopsy.

Roentgenological Contrast Demonstration of Spleen and Liver (Zur Kontrastuntersuchung von Milz und Leber.) By H. BAUMANN and C. SCHILLING. (Klin. Wchnschr., 1931, x, 1249-1252.)

The principle of contrast demonstration proposed by Radt and investigated also by Oka is the basis of the present study. In this method the contrast substance introduced in colloidal state into the organism parenterally, is taken up by the reticulo-endothelial cells in finely granular form. In further study of this method the authors made use of a preparation containing 25 per cent thorium dioxide (ThO_2) which was miscible with all body fluids without precipitation. It was found that 1 c.c. of this 25 per cent thorium dioxide preparation was sufficient to produce a positive shadow of liver and spleen in a 2 kgm. rabbit. The shadow reached its maximum depth in two hours. Through further injections and in larger amounts (3 c.c. twice a day until 12 c.c. had been given) a much deeper shadow resulted. Histological study of a few animals showed very fine glistening particles in the reticulo-endothelial cells. After twenty-four hours the Kupffer's cells of the liver were found greatly swollen and in a rabbit which had received 12 c.c. of the thorium preparation they were as large as liver cells fourteen days after the last injection. There was no necrosis of liver cells found. This method was made use of successfully in studying the effect of drugs upon the size of the spleen and liver in rabbits and dogs.

Studies in Asphyxia. I. Neuropathology Resulting from Comparatively Rapid Carbon Monoxide Asphyxia. By JOHN CHORNYAK and R. R. SAYERS. (Public Health Reports, 1931, xlvi, 1523-1530.)

It has been repeatedly observed that many cases of carbon monoxide poisoning have a fatal termination even though respiration has been induced and the carbon monoxide removed from the blood. The series of investigations, of which this is the first report,

have in view obtaining fundamental information as to the response of the animal organism to such an asphyxial environment, looking toward devising a therapeutic procedure for apparently moribund cases of carbon monoxide poisoning. This first study deals with the neuropathology found in four dogs after continuous exposures of 20 to 30 minutes to 0.6 per cent carbon monoxide by volume in air. These conditions produce 75 to 85 per cent carbon monoxide hemoglobin and result in death at the end of the period of exposure. The changes found in these animals were fairly constant and were lacking in control material. The brain, as a whole, showed a severe perivascular and perineuronal edema. This was most marked in the corpus striatum, the cortex, and the dorsal motor nucleus of the vagus nerve. Congestion was marked throughout and there were a few petechial hemorrhages in the corpus striatum and cortex. A few lymphocytes and leucocytes were found in the perivascular spaces. Many nerve cells were swollen, distorted and vacuolated and showed marked changes in the Nissl material. Some cells were shrunken and stained diffusely while others showed varying degrees of chromatolysis. The most serious lesion produced by this type of asphyxia appeared to be the edema of the dorsal motor nucleus of the vagus and the adjacent area in the medulla oblongata.

Insulin Resistant Diabetes. By MARCEL LABBÉ. (Rev. belge des Sci. méd., 1931, iii, 465-491.)

Those paradoxical cases in which insulin fails to give the usual effects and which are spoken of as "insulin-resistant" appear to be frequent to some observers and rare to others. A majority of the published examples of insulin resistance represent errors in interpretation growing out of poor management in connection with insulin therapy. True insulin resistance exists but it is rare. It appears in an incomplete form in certain endocrine diabetics, and in a complete form in certain cases of insular diabetes without any known explanation. Its existence may be established, (a) if in a diabetic on a suitable régime insulin fails to depress the level either of glycosuria or ketosis; (b) if in a diabetic who is adhering to a suitable régime excessive amounts of insulin are required to prevent glycosuria and acidosis, and to maintain nutritional equilibrium, or (c) if the sub-cutaneous or intravenous injection of insulin in the amount usually employed to demonstrate a hypoglycemia fails to lower the level of glycemia to the degree usually seen in the diabetic. Rigid application of these criteria will make it possible to exclude the false examples of insulin resistance and to recognize the true condition in both its incomplete and complete forms.

Effect on Life Insurance Mortality Rates of Rejection of Applicants on the Basis of Medical Examination. By ROLLO H. BRITTEN. (Public Health Reports, 1931, xlvi, 46-62.)

In connection with a joint investigation on occupational mortality by the Actuarial Society of America and the Association of Life Insurance Medical Directors data were secured on ordinary insurance business during the years 1915 to 1926, involving more than one-half billion dollars in death claims. Analysis of this large mass of information suggests that the insurance medical examination results in a lower mortality during the earlier insurance years as compared with persons of the same age who have held policies for a longer time. The duration of this selective effect appears to last for three or four years for all causes, except possibly at the highest age levels. For tuberculosis and heart disease it is possible that the selective effect is of much longer duration. The mortality rates in the first years of policy life are only about two-thirds of those after the effect of selection has disappeared. These results would seem to have an important and positive bearing upon the question of the value of periodic health examinations.

Reviews

Physical Diagnosis. By WARREN P. ELMER, B.S., M.D.; Associate Professor of Clinical Medicine, Washington University, School of Medicine; Assistant Physician to Barnes Hospital; Physician-in-Charge Missouri Pacific Hospital; Consulting Physician to Jewish Hospital, St. Louis: and W. D. ROSE, M.D., Late Associate Professor of Medicine in the University of Arkansas, Little Rock, Arkansas. 903 pages, 337 illustrations. The C. V. Mosby Company, St. Louis, Mo., 1930. Price $10.00.

This book is a very complete revision of the work by W. D. Ross on the same subject. There has been a rearrangement of the subject matter with a division between the technic and the findings in the physical examination of the normal body (Part I, 530 pages), and the physical diagnosis of disease (Part II, 338 pages). This difference may be clearly understood if Part I be thought of as General Physical Diagnosis in contrast to the Special Physical Diagnosis of Part II. Throughout the first division there are numerous references to pathologic conditions and the technic of eliciting those physical signs which are produced only in pathologic conditions is also included in this section. Of necessity, since this is a textbook suitable for use in medical schools, the level of approach is that of the second year medical student. Nevertheless the more advanced student, the intern, and the practitioner will find this book of very great value. The reviewer feels that it should not be necessary to include such information as that the heart has "an auricle and a ventricle upon either side" and that "the left auricle and ventricle contain arterial blood, while the right auricle and ventricle contain venous blood" in a textbook on physical diagnosis. The anatomist and physiologist must have accomplished something in their teaching. The incidence of primary carcinoma of the lung as given (page 62) is less than one-half that known to exist at the present time. Taken as a whole, however, this is a very useful and very well written book. The illustrations are extremely well chosen. They show precisely how certain procedures are to be carried out. Surface relations are illustrated by both photographs and skeletal charts arranged in pairs in a very instructive manner. No opportunity is lost to teach clinical pathology on practically every page.

Selected Readings in the History of Physiology. By JOHN FARQUHAR FULTON, M.D., formerly Fellow of Magdalen College, Oxford; Sterling Professor of Physiology, Yale University. xx + 317 pages, 60 illustrations. Charles C. Thomas, Springfield, Ill., and Baltimore, Md., 1930. Price, $5.00.

This interesting work is a source book for the history of Physiology. Eighty-five selections have been chosen from original sources and are presented in the original English, if the text first appeared in that language. Otherwise contemporary English translations are used where such exist. Each is preceded by a brief explanatory note, in part biographical and in part indicating the significance of the work quoted in connection with contemporary knowledge. The selections chosen are grouped in eight main divisions or chapters, corresponding to the usual divisions of didactic Physiology. Within each group the arrangement is chronological. The choice of the individual readings might well be a subject for discussion among physiologists and medical historians, less in respect to the investigators included as to whether the paragraphs selected are the most important or the most significant among their writings. Individual viewpoint will influence opinion on this score. To the reviewer the choice seems excellent in subject

matter and in literary value. Interest is well sustained throughout. The illustrations are not the familiar ones from medical histories, and the liberal use of reproductions of title pages will appeal to the book lover. This book should be read by every medical student as collateral reading in the second half of his course in physiology. Many practitioners will appreciate it and it should be a popular gift book among a large group interested in the biological sciences.

Protozoan Parasitism of the Alimentary Tract: Pathology, Diagnosis, and Treatment. By KENNETH M. LYNCH, M.D., Professor of Pathology, Medical College of the State of South Carolina, Charleston, South Carolina. xviii + 258 pages, 37 illustrations. The MacMillan Company, New York City, 1930. Price, $3.75.

To serve as a connecting link between systematic protozoology and clinical medicine in respect to the protozoan parasites of the alimentary tract is the purpose of this monograph. The author properly recognizes that most practitioners of medicine are concerned only with the pathogenic significance, recognition and treatment of a limited number of important parasites. Technical descriptions, such as the professional protozoologist would require, are largely omitted or rewritten in a manner understandable to those doing medical laboratory work. Procedures are outlined for routine stool examinations. Especially to be commended are the strongly put warnings against assigning unwarranted importance to fairly constant protozoan inhabitants of the intestinal tract when scientific evidence of pathogenic significance is lacking. More carefully systematized descriptions of gross and microscopical pathology would be useful. The claims of Kofoid and his associates in respect to finding *Endamoeba histolytica* in the tissues of joints in arthritis deformans and in the lymph nodes in Hodgkin's disease are properly discredited. Treatment is fully outlined in respect to those organisms known to be pathogenic. This book will correct many false impressions which are commonly held.

Discovering Ourselves; A View of the Human Mind and How it Works. By EDWARD A. STRECKER, A.M., M.D., Professor of Nervous and Mental Diseases, Jefferson Medical College, Philadelphia; and KENNETH E. APPEL, Ph.D., M.D., Assistant Professor of Psychiatry, School of Medicine, University of Pennsylvania. xiii + 306 pages, 28 illustrations. The MacMillan Company, New York City, 1931. Price, $3.00.

This is a book for the individual, about himself; and it is a book with a mission. Although it deals with the fundamentals of normal and abnormal psychology, it is never abstruse, or unclear, or dull. It can be read by every medical man and every intelligent layman, too, with pleasure and profit. It succeeds in avoiding the specialized terminology of psychology, substituting well understood and yet scientifically accurate expressions for the vernacular of the specialist. The authors thus state their objective: "If the stakes in the game of physical hygiene are health and life, then the stakes in the game of mental hygiene are even higher; efficiency or inefficiency; success or failure; happiness or unhappiness; replete, satisfying, and worth while lives or empty, unsatisfactory, and pathetic existences; sanity or insanity. It is to the realization of the constructive potentialities of the human mind that this book is dedicated." The physician who has a sympathetic grasp of its content will find that he can prescribe this book with profit to certain of his patients.

College News Notes

The American College of Physicians began to publish an official journal, known as "Annals of Clinical Medicine", July, 1922. It is interesting to note that the following members contributed to that number:

Dr. James M. Anders, (Master)
Dr. Sydney R. Miller, (Fellow)
Dr. Leonard M. Murray, (Fellow)
Dr. C. C. Bass, (Fellow)
Dr. Louis M. Gompertz (Deceased), (Associate)
Dr. William Carpenter MacCarty, (Fellow)
Dr. Leo L. Hardt, (Fellow)

Dr. Vernon C. Rowland (Fellow), Cleveland, was the official representative of the American College of Physicians, appointed by the President, on the occasion of the formal dedication of the Lakeside Hospital group at Cleveland, June 7, when Western Reserve University brought to completion its $15,000,000 Medical Center. From all sections of the country delegates of the leading scientific, medical, educational, social and civic organizations came to attend the ceremonies and pay tribute to this institution. The address of dedication was delivered by Dr. Hans Zinsser, Professor of Bacteriology of Harvard University Medical School. Later, Western Reserve University conferred upon Dr. Zinsser the honorary degree of Doctor of Science. This degree was also conferred upon Dr. David Marine (Fellow), Director of Laboratories, Montefiore Hospital, and Assistant Professor of Pathology at Columbia University College of Physicians and Surgeons; Dr. Samuel C. Harvey, Professor of Surgery, Yale University School of Medicine; Dr. Evart A. Graham, Professor of Surgery, Washington University School of Medicine; Dr. Alphonse R. Dochez, Professor of Medicine, Columbia University College of Physicians and Surgeons; and Dr. Alfred Newton Richards, Professor of Pharmacology at the University of Pennsylvania School of Medicine. The degree of Doctor of Laws was conferred upon Dr. Henry A. Christian (Fellow), Hersey Professor of the Theory and Practice of Physic at Harvard University Medical School, and on Dr. James Ewing, Professor of Pathology, Cornell University Medical College.

Dr. William Gerry Morgan (Fellow), Washington, D.C., was recently elected a member of the Board of Regents of Georgetown University.

Dr. E. J. G. Beardsley (Fellow), Philadelphia, gave the graduation address of the Medical Field Service School at Carlisle Barracks, Carlisle, Pa., May 30, 1931, upon "Service Ideals, the Medical Profession and the Public".

On June 17, 1931, Dr. Beardsley addressed the members of the Hazleton (Pa.) Medical Society upon "Medical Art in Connection with Cardiovascular Disorders".

Dr. Frank B. Cross (Fellow), Brooklyn, on May 19, addressed the Medical Society of the County of Kings on "Stimulation of the Renal Secretion".

"What the Doctor of Internal Medicine Expects from the Occupational Therapists" was the subject of an address delivered by Dr. Walter P. Anderton (Fellow), New York, N. Y., May 22, before the Brooklyn Society of Internal Medicine.

Dr. Henry M. Moses (Fellow) Brooklyn, N. Y., read a paper on "Carcinoma of the Lung", May 12, at the meeting of the Medical Society of Bay Ridge.

Dr. William J. Kerr (Fellow), San Francisco, was included among the guest speak-

ers at the annual meeting of the Canadian Medical Association, June 22-26. Dr. Kerr's subject was "Coronary Occlusion".

Dr. Israel M. Rabinowitch (Fellow), Montreal, addressed the same meeting on "Diabetes".

Dr. Anton J. Carlson (Fellow), Chicago, and Dr. Fred Moore (Fellow), Des Moines, are members of the Committee appointed to follow up the findings of the medical service section of the White House Conference on Child Health and Protection, as announced by Secretary Ray Lyman Wilbur on May 20. Dr. Wilbur is Honorary Chairman of this Committee. The findings of this Committee will be distributed to those organizations that are striving to improve the health of children.

Dr. Thomas B. Futcher (Fellow), Baltimore, and Dr. James H. Means (Fellow), Boston, were elected President and Secretary, respectively, of the Association of American Physicians at its annual meeting on May 6.

Dr. Cyrus C. Sturgis (Fellow), Ann Arbor, was elected Secretary of the American Society for Clinical Investigation on May 4.

The following Fellows of the College addressed the American Heart Association on June 9, during its seventh annual meeting, in Philadelphia:

Dr. Fred M. Smith, Iowa City
Dr. Stewart R. Roberts, Atlanta
Dr. John H. Musser, New Orleans
Dr. David Riesman, Philadelphia
Dr. James B. Herrick, Chicago
Dr. Paul D. White, Boston
Dr. Emanuel Libman, New York

Dr. Elliott P. Joslin (Fellow), Boston, recently addressed the George Washington University Medical School on diabetes.

Dr. William Engelbach (Fellow), New York, on June 20 addressed the Schuyler County (Ill.) Medical Society on "Diagnosis and Treatment of Endocrine Disorder".

Dr. Fred M. Smith (Fellow), Iowa City, delivered an address on "Arteriosclerotic Heart Disease", April 9, before the Linn County (Iowa) Medical Society.

Dr. Jeannette Dean Throckmorton (Fellow), Des Moines, was recently elected Treasurer of the Iowa State Medical Women Society.

Dr. George R. Minot (Fellow), Boston, presented a paper on "Adequate Treatment of Anemia" before the Plymouth District Medical Society on May 21 at Abington.

Dr. Paul D. White (Fellow), Boston, spoke on "Precordial Pain and Tenderness" at a meeting of the cardiac course of the New England Heart Association on May 13.

Dr. Frank Vander Bogert (Fellow), Schenectady, used as his subject "Feeding of Sick Children" in an address, May 12, before the Medical Society of the County of Washington (New York).

Dr. Lawrason Brown (Fellow), Saranac Lake, and Dr. James B. Herrick (Fellow), Chicago, are on the tentative program of the Oklahoma City Clinical Society, which will hold its annual fall conference November 2-5.

The following Fellows of the College addressed the Garfield County (Okla.) Medical Society, April 9, as indicated:

Dr. Porter P. Vinson—"Diagnosis and Treatment of Cardiospasm";

Dr. John H. Musser—"Acute Infections";

Dr. Charles A. Elliott—"Blood Pressure".

Dr. Donald R. Ferguson (Fellow), Philadelphia, Clinical Professor of Medicine at the Hahnemann Medical College, was recently elected President of the Philadelphia County Homeopathic Medical Society.

Dr. Franklin F. Murdoch (Fellow), Lieutenant Commander, U. S. Navy, was appointed during June, Professor of Tropical Medicine at the George Washington University Medical School.

Dr. James Craig Small (Fellow), Philadelphia, was elected an honorary member of Phi Beta Kappa, Iota Chapter of Pennsylvania, on June 6, 1931, the twentieth anniversary of his graduation from Gettysburg College.

Dr. M. Murray Peshkin (Fellow), New York, delivered a paper on "A Dry Pollen Ophthalmic Test in Asthma and Hay Fever Patients Negative to Cutaneous Tests", June 9, before the American Association for the Study of Allergy at Philadelphia. The technic of the dry pollen eye test and the various positive reactions in natural colors were shown in the Allergy Section of the Scientific Exhibit of the American Medical Association during the week of June 8.

Dr. Michael Vinciguerra (Fellow), Elizabeth, N. J., was recently appointed Assistant in Neurology at Columbia University and Assistant Visiting Physician in Neurology at Columbus Hospital.

Dr. Mortimer Warren (Fellow), Portland, Maine, was awarded the degree of Doctor of Science by Bowdoin College on June 18, 1931.

Dr. Fred M. Smith (Fellow), Iowa City, was elected President of the Iowa Heart Association on May 15.

Dr. Alexander G. Brown, Jr. (Fellow), Richmond, Va., participated in the unveiling of a tablet to the honor of Dr. William Brown, his great-great-great-grandfather who was the Surgeon General of the Continental Army during the American Revolution. The unveiling exercises took place June 14 at 212 S. Fairfax Street, Alexandria, Va., the bronze tablet being placed on the old home of Dr. Brown.

Dr. John A. Macgregor (Fellow), London, Ont., was the recipient of the degree of Doctor of Laws, conferred by the Senate of the University of Western Ontario at the June Convocation. Dr. Macgregor is Professor Emeritus of Medicine of the University of Western Ontario Faculty of Medicine.

Dr. Ross V. Patterson (Fellow), Philadelphia, Dean of Jefferson Medical College and President of the Medical Society of the State of Pennsylvania, received the degree of Doctor of Science from La Salle College on May 24.

Dr. Horton R. Casparis (Fellow), Nashville, delivered an address on "Tuberculosis in Children" on May 28 at the first of four joint meetings to be held by the Medical Societies of Roane, Monroe, Loudon and McMinn Counties (Tenn.).

At the recent annual meeting of the West Virginia State Medical Association, Dr. Albert H. Hoge (Fellow), Bluefield, was elected President. Dr. Hoge will assume office on January 1, 1932.

Dr. Walter Simpson (Fellow), Dayton, and Dr. Cyrus C. Sturgis (Fellow), Ann Arbor, addressed the Pacific Northwest Medical Association, June 25-27, at Seattle on "Tularemia" and "Treatment of Pernicious Anemia", respectively.

At the annual meeting of the American Climatological and Clinical Association, on May 8, Dr. Louis Hamman (Fellow), Baltimore, was elected President.

During the recent meeting in Philadelphia of the Association for the Study of Allergy, Dr. Albert H. W. Caulfeild (Fellow), Toronto, was elected President-Elect, and Dr. Warren T. Vaughan (Fellow), Richmond, was elected Secretary-Treasurer.

Dr. Lyell C. Kinney (Fellow), San Diego, participated in a symposium on medical economic problems, which was presented before the San Diego County Medical Society on June 9.

Dr. Oscar M. Gilbert (Fellow), Boulder, Colo., addressed the Boulder County Medical Society, June 11, on "Coronary Sclerosis in Diabetes".

Dr. Lester R. Dragstedt (Fellow), Chicago, gave an illustrated lecture on "Acute

Intestinal Obstruction" before the Twelfth District Medical Society, May 26, at Fort Wayne, Indiana.

Dr. Frederick G. Banting (Fellow), Toronto, Ont., spoke before the students and faculty of the University of Michigan Medical School, May 8, on "The History of Insulin".

At the clinic of the Kansas City Southwest Clinical Society, June 9, Dr. Peter T. Bohan (Fellow), Kansas City, spoke on "Intercostal Neuralgia Simulating Visceral Disease".

Dr. Henry Kennon Dunham (Fellow), Cincinnati, was re-elected President of the Ohio Public Health Association on June 4.

Dr. John H. Peck (Fellow), Des Moines, was elected one of the Vice Presidents of the National Tuberculosis Association at its meeting in Syracuse on May 11-14.

Dr. James B. Herrick (Fellow), Chicago, member of the Class of 1888, Rush Medical College, acted as Toastmaster at the annual dinner of the faculty and alumni during the Rush Homecoming Week.

Lieutenant Colonel W. Lee Hart (Fellow), has been transferred from the Army War College to Omaha, seventh corps area.

Captain John D. Brumbaugh (Associate), has retired from the Medical Corps of the U. S. Army due to incapacitation from active service.

Lientenant Colonel William L. Sheep (Fellow), has been assigned to Balboa Heights, Canal Zone, as has also Lieutenant Colonel Ernest R. Gentry (Fellow).

The following Fellows of the College held a Clinic for the physicians of South Carolina at the South Carolina State Sanatorium, Columbia, July 29-30:

Dr. R. P. McCain, Sanatorium, N. C.
Dr. Paul Ringer, Asheville, N. C.
Dr. J. B. Sidbury, Wilmington, N. C.

Dr. Thomas Addis (Fellow), Stanford, University Medical School, San Francisco, has been selected to deliver the William Sydney Thayer lecture at Johns Hopkins University School of Medicine this year.

At the Texas State Medical Society's meeting in May, the following Fellows were among the out-of-state speakers:

Dr. Clifford A. Barborka, Rochester, Minn.

Dr. William C. MacCarty, Rochester, Minn.

Dr. Tom B. Throckmorton, Des Moines, Iowa.

Dr. Ralph Pemberton (Fellow), Philadelphia, is a charter member of the newly organized American Society of Physical Medicine. The aims of this organization are to improve the practice of physical medicine, promote research, encourage clinical investigation and advance the teaching of physical medicine. The Officers are:

Dr. John S. Coulter, Chicago, President;
Dr. K. G. Hansson, New York, Vice President;
Dr. Willis S. Peck, Ann Arbor, Secretary and Treasurer.

Dr. George Herrmann (Fellow), formerly Associate Professor of Medicine at Tulane University of Louisiana School of Medicine, will go to the University of Texas as Professor of Clinical Medicine at the opening of the fall term. His new address is: The John Sealy Hospital, 816 Avenue B, Galveston, Texas.

Dr. John E. Walker (Fellow), Opelika, Ala., is the author of an article on "The Germicidal and Therapeutic Applications of Soaps", which appeared in the Journal of the American Medical Association, July 4, 1931.

Dr. Walker addressed the Chattahoochee Valley Medical and Surgical Association at Albany, Ga., July 15, on "The Clinical Recognition of the Cardiac Arythmias".

Dr. A. G. Schnack (Fellow), Honolulu, Hawaii, and Dr. K. S. Davis (Fellow), Los Angeles, Calif., are authors of "Chronic

Appendicitis" and "Atypical Bone Tumors: with Presentation of Two Cases", respectively, appearing in the July issue of Radiology.

Dr. William Egbert Robertson (Fellow), Philadelphia, was one of the speakers at the dedication of the Quakertown Community Hospital, Quakertown, Pa., on June 21. The hospital was erected at a cost of $200,000, raised by public subscription.

Dr. Elmer Funk (Fellow), Philadelphia, was Toastmaster at the Alumni Dinner of Jefferson Medical College, July 3, when a large number of the Alumni celebrated the 160th annual Ex-Interns' Day and Alumni Day. Dr. Ross V. Patterson (Fellow), was one of the speakers, and, as Dean of Jefferson Medical College, accepted an oil portrait of Dr. John M. Fisher, Associate Professor of Gynecology, the oldest ex-intern of Jefferson Hospital.

Among Fellows of the College who have recently been appointed to the Abington (Pa.) Memorial Hospital are the following:

Dr. Henry L. Bockus, Professor of Gastro-enterology of the University of Pennsylvania Graduate School of Medicine;

Dr. John Eiman, Assistant Professor of Pathology, University of Pennsylvania Graduate School of Medicine;

Dr. George Morris Piersol, Professor of Medicine, University of Pennsylvania Graduate School of Medicine;

Dr. G. Harlan Wells, Professor of Medicine, Hahnemann Medical College;

Dr. William D. Stroud, Associate Professor, Diseases of the Heart, University of Pennsylvania Graduate School of Medicine;

Dr. Harry B. Wilmer, Associate Professor of Medicine, University of Pennsylvania Graduate School of Medicine.

Dr. Arthur W. White (Fellow), Oklahoma City, Okla., is author of an article entitled "Clinical Aspects of Gastric and Duodenal Ulcer" in the July issue of the Journal of the Oklahoma State Medical Association.

Doctors Claiborne T. Smith (Fellow), and William Bernard Kinlaw (Fellow), both of Rocky Mount, N. C., were the recipients of the Moore County (N. C.) Medical Society's medal for having presented the best paper at the 1930 meeting of the North Carolina State Medical Society, the medal being presented during the last annual meeting of the State Society at Durham.

Dr. Charles G. Jennings (Fellow), Detroit, was elected Honorary President of the Medical Alumni Association of the Detroit College of Medicine and Surgery on June 18, the occasion of its 61st Reunion. Dr. Jennings is the oldest graduate of the College, having been graduated in 1879.

Dr. Ernest H. Falconer (Fellow) and Dr. Hans Lisser (Fellow), both of San Francisco, were recently advanced from Associate Clinical Professors of Medicine to Clinical Professors of Medicine in the University of California Medical School.

Dr. Thomas B. Futcher (Fellow) and Dr. Louis Hamman (Fellow), both of Baltimore, were among the invited speakers before the Mahoning County Medical Society at Youngstown on June 18, the occasion of its 5th annual postgraduate day. Dr. Futcher delivered two addresses, one on "The Problem of Arthritis in General Practice" and the other, "Manifestations of Hyperfunction and Hypofunction of the Endocrine Glands". Dr. Hamman also delivered two addresses, one on "Diagnosis of Obscure Fevers", and the other, "Diagnosis of Coronary Occlusion".

Dr. Willard C. Rappleye (Fellow), Dr. Walter W. Palmer (Fellow), and Dr. Arthur F. Chace (Fellow), all of New York City, have been appointed by President Nicholas Murray Butler, of Columbia University, members of the Administrative Board of Postgraduate Studies in Medicine, to have general control of all postgraduate instruction in medicine under the auspices of the University. The New York Postgraduate Medical School and Hospital became on July 1, the Postgraduate School of Medicine of Columbia University.

Dr. Waller S. Leathers (Fellow), Nashville, addressed the Christian County Medical Society at Hopkinsville, Ky., June 16, on "Significant Achievements in the Field of Preventive Medicine".

Dr. Leathers is Dean and Professor of Preventive Medicine and Public Health at Vanderbilt University School of Medicine. He was recently re-elected President of the National Board of Medical Examiners.

Dr. Charles E. Homan, Jr. (Fellow), Chattanooga, addressed the Chattanooga and Hamilton County Medical Society, June 4, on "Spastic Colon".

Dr. Karl H. Doege (Associate), Marshfield, Wis., addressed the Wood County (Wis.) Medical Society, June 25, on "Some Aspects of Acute Rheumatic Fever".

Dr. Hyman I. Goldstein (Associate), Camden, N. J., read a paper before the American Therapeutic Society, held at Atlantic City during June, on "Streptococcic Faucitis with Erythema Nodosum and Erythema Multiforme Exudativum: Diagnosis and Treatment".

Dr. H. Sheridan Baketel (Fellow), Jersey City, spoke on "Present Trends in the Practice of Medicine" at a meeting of the Fifth Councilor District of the Medical Society of New Jersey, at Atlantic City, April 10th. On June 24th he spoke to the physicians of the Lehigh Valley at Bethlehem, Pa., on the "Economics of Medical Practice."

Dr. Jacob M. Cahan (Fellow), Philadelphia, addressed the local Medical Inspectors of Public Schools on the subject of Heart Disease in Children, presenting cases with various lesions, on June 30th, 1931.

The American Congress of Physical Therapy

The tenth anniversary session of the American Congress of Physical Therapy will be held October 5, 6, 7, and 8, 1931, at the Hotel Fontenelle, Omaha, Nebraska. A preliminary program and other information can be obtained from the American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago, Ill.

Acknowledgment is made of the following gifts of reprints by members of the College to the College Library:

Dr. Clarence H. Boswell (Fellow), Rockford, Ill.—1 reprint.

Dr. Arthur C. Clasen (Fellow), Kansas City, Mo.—4 reprints.

Dr. M. J. Fein (Associate), Brooklyn, N. Y.—1 reprint.

Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint.

Dr. John F. W. Meagher (Fellow), Brooklyn, N. Y.—16 reprints.

Dr. Roy D. Metz (Fellow), Detroit, Mich.—1 reprint.

Dr. Karl Rothschild (Associate), New Brunswick, N. J.—2 reprints.

Dr. Carl V. Vischer (Fellow), Philadelphia, Pa.—1 reprint.

Dr. George L. Waldbott (Fellow), Detroit, Mich.—2 reprints.

OBITUARIES

DOCTOR REYNOLD WEBB WILCOX

Dr. Reynold Webb Wilcox (Fellow), first President and charter member of the American College of Physicians, died at his home in Princeton, N. J., June 6, 1931; aged, 75 years.

Dr. Wilcox was born in Madison, Conn. He attended the Lee's Academy for his elementary education, and graduated from Yale University with the degree of Bachelor of Arts in 1878. He received his medical training at Harvard University Medical School, graduating in 1881. He held the honorary degrees of Master of Arts from Hobart College in 1881; Doctor of Laws from Maryville College in 1892; and Doctor of Civil Law from Wittenberg College in 1915. He did postgraduate work at the New York Postgraduate Medical School and Hospital, in which institution he later became Professor of Medicine. He was formerly on the Staffs of St. Mary's Hospital (New York), Ossining Hospital (New York), Eastern Long Island Hospital (Greenport, N. Y.), Nassau Hospital (Mineola) and the New Jersey State Hospital (Greystone Park). He was the author of more than three hundred and fifty articles published in various American journals. He was also author of "Materia Medica and Therapeutics", of which ten editions were published; also "Treatment of Disease", five editions; and several other books.

He was a member of the Revision Committee of the U. S. Pharmacopoeia in 1900-1910.

His memberships in scientific societies included the Harvard Medical Society, Medical Association of Greater New York, American Academy of Medicine, American Association of Military Surgeons, Society of Medical Jurisprudence, American Association on Medical Jurisprudence, American Association for Advancement of Science, American Therapeutic Society, Connecticut State Medical Association, American Medical Association, American Congress on Internal Medicine, and others.

Dr. Wilcox, with a small group of Internists, conceived the idea of the organization of the American College of Physicians, for which they secured a charter on May 11, 1915, under the laws of the State of Delaware. He became the first President, continuing in office until 1922. In recent years, he had been more or less incapacitated in health, but maintained an active and personal interest in the activities and work of the College.

DOCTOR ARTHUR CLIFFORD SELMON

Dr. Arthur Clifford Selmon (Fellow), Battle Creek, Mich., died suddenly, May 16, of chronic myocarditis; aged, 53 years.

Dr. Selmon was born near Columbus Junction, Iowa, in 1877. He attended the Iowa State Normal School, then entered the Keokuk Medical College from which he later transferred to the American Medical Missionary College, receiving the degree of Doctor of Medicine in 1902. In 1903, he began missionary work in China, Honan

Province, where he remained for ten years. For eleven additional years he was engaged in missionary work in Shanghai as Internist to the Shanghai Sanitarium. During this time, he, with the help of Chinese scholars, edited a book on "Health and Longevity", written in Chinese. This book is a contribution to the cause of disease prevention in that country where, lacking health departments, the individual was the only approach to the problem. About fifty thousand copies of this book in Chinese have been distributed. It has been translated into fifteen other languages and a translation into Arabic is contemplated.

He pursued postgraduate study in Hematology at Tulane University of Louisiana School of Medicine, and in Blood Chemistry, Physical Diagnosis and Internal Medicine at the New York Postgraduate Medical School. In 1925, he became Staff Physician of the Kellogg Company, Battle Creek, which position he held until the recent creation of the W. K. Kellogg Foundation. During the five years that Dr. Selmon was in charge of the Kellogg Company Hospital, the average for lost time because of sickness or injury on the part of Kellogg employees was reduced to such a degree as to establish a record for industries of the United States. Many departments were added to the hospital under Dr. Selmon's direction, until it is now one of the model industrial hospitals of the world.

As Associate Medical Director of the W. K. Kellogg Foundation, Dr. Selmon was enthusiastically and energetically organizing the plans of carrying out the purposes of the Foundation, including the studying of the childhood causes which are blighting influences in life later on; as perhaps in his own case, an early typhoid fever may have been a factor in his untimely death.

(Furnished by Stuart Pritchard, M.D., F.A.C.P., Battle Creek, Mich.)

DOCTOR HORACE HOWARD JENKS

Dr. Horace Howard Jenks (Fellow), Philadelphia, died July 6, 1931, of bronchopneumonia; aged fifty-three years.

Dr. Jenks was born at Ashbourne, Montgomery County, Pa., June 7, 1878. He attended Haverford College, from which he graduated with the degree of Bachelor of Arts in 1900, whereupon he entered the University of Pennsylvania School of Medicine, from which he graduated in 1904 with the degree of M.D. Dr. Jenks was Associate in Pediatrics, University of Pennsylvania School of Medicine from 1927 to 1929, and Assistant Professor of Pediatrics in the University of Pennsylvania Graduate School of Medicine from 1926 to date of his death. He was Assistant Visiting Physician, 1924 to 1930, and Visiting Physician, 1930 to the time of his death, to the Children's Hospital; Visiting Physician to St. Christopher's Hospital for Children since 1927, and Medical Director of the Associated Medical Clinics since 1920.

Dr. Jenks was a Fellow of the Philadelphia College of Physicians and of the American Medical Association. He was elected a Fellow of the American College of Physicians on November 11, 1930. Other memberships included the Philadelphia Pediat-

ric Society, the Philadelphia County Medical Society, the Pennsylvania State Medical Association and the American Pediatric Society. Dr. Jenks was honored by election to office in several of these organizations. He had served as President of the Philadelphia Pediatric Society, and at the time of his death was Chairman of the Certified Milk Commission of the Philadelphia Pediatric Society. To this latter position, he brought his wealth of experience and ability as an executive and organizer, which he had demonstrated so thoroughly in his connection with the Associated Medical Clinics, organized and developed to a high degree of efficiency by him. Quiet in dignity and reserved in manner, Dr. Jenks had a host of friends not only among his patients but also among his colleagues and associates. In his sudden death, the medical profession has lost an earnest and conscientious member; the community, a citizen of greatest worth; and his family, a husband and father whose love will be cherished forever.

(Furnished by Alvin E. Siegel, M.D., F.A.C.P., Philadelphia, Pa.)

DOCTOR HARRY M. HALL

Dr. Harry M. Hall (Fellow), Wheeling, W. Va., died, June 6, 1931; aged, 53 years.

Dr. Hall was born in Wheeling and received his elementary training in the Wheeling Public Schools. He attended Western Reserve University of Medicine, from which he received the Degree of Doctor of Medicine in 1898. For many years, he was a member of the Staff and Instructor of Nurses in Principles of Medicine of the Ohio Valley General Hospital. At the time of his death, he was Director of the West Virginia Tuberculosis and Health Association and Associate Editor of the West Virginia Medical Journal. He was Councilor-at-large of the West Virginia State Medical Association, having been President of that organization in 1929-1930. He became a Fellow of the American College of Physicians on November 17, 1928. He was also a member of the Ohio County Medical Society, and a Fellow of the American Medical Association.